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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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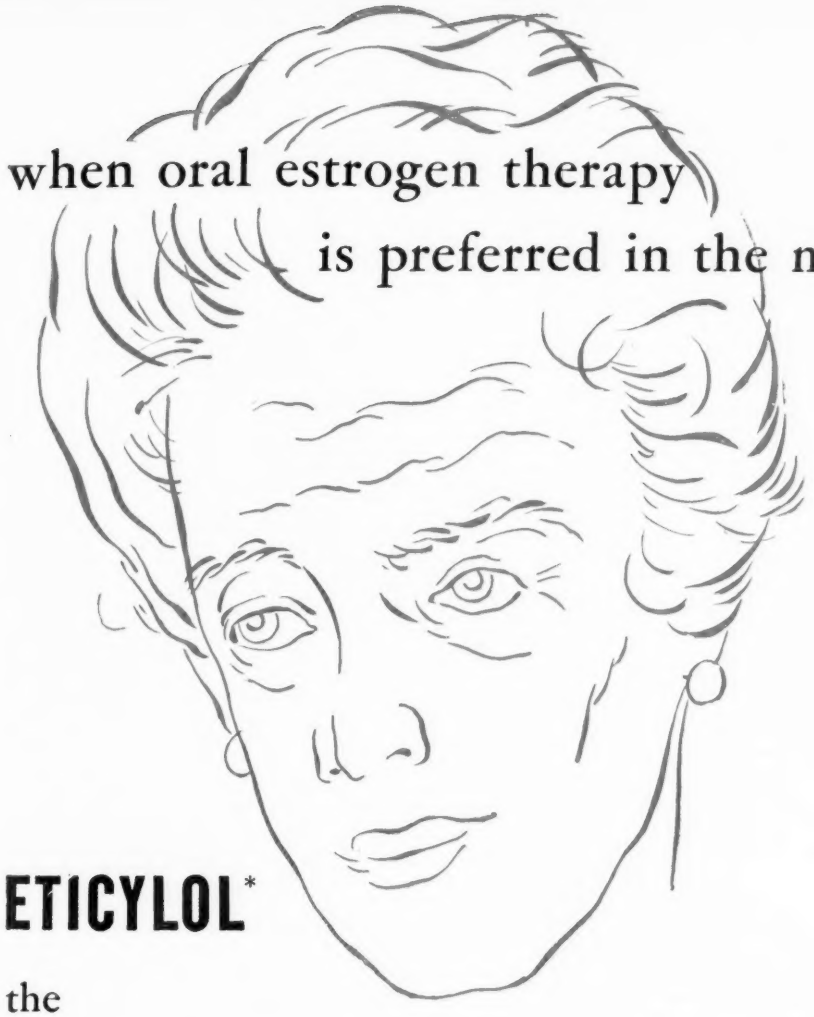

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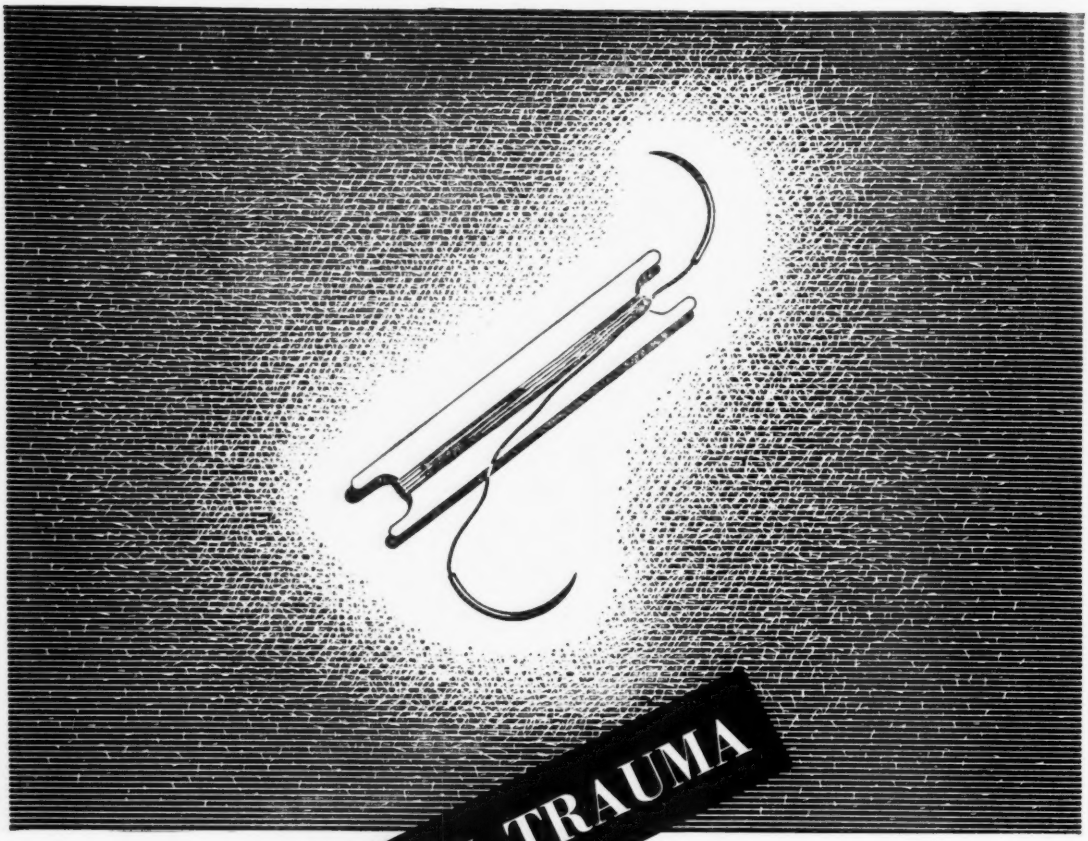

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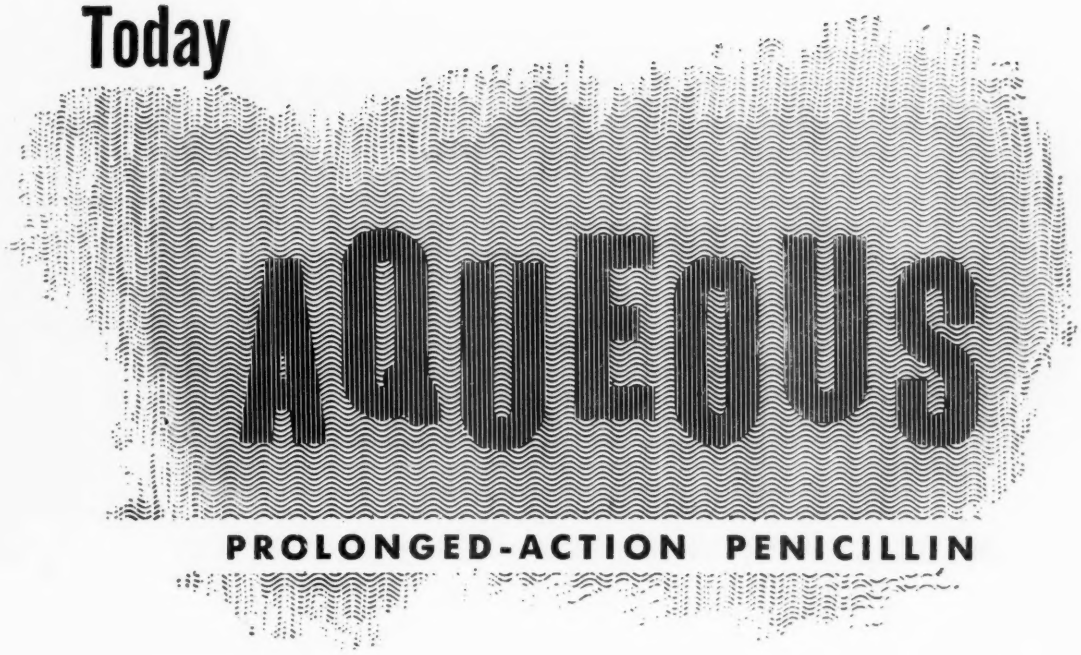

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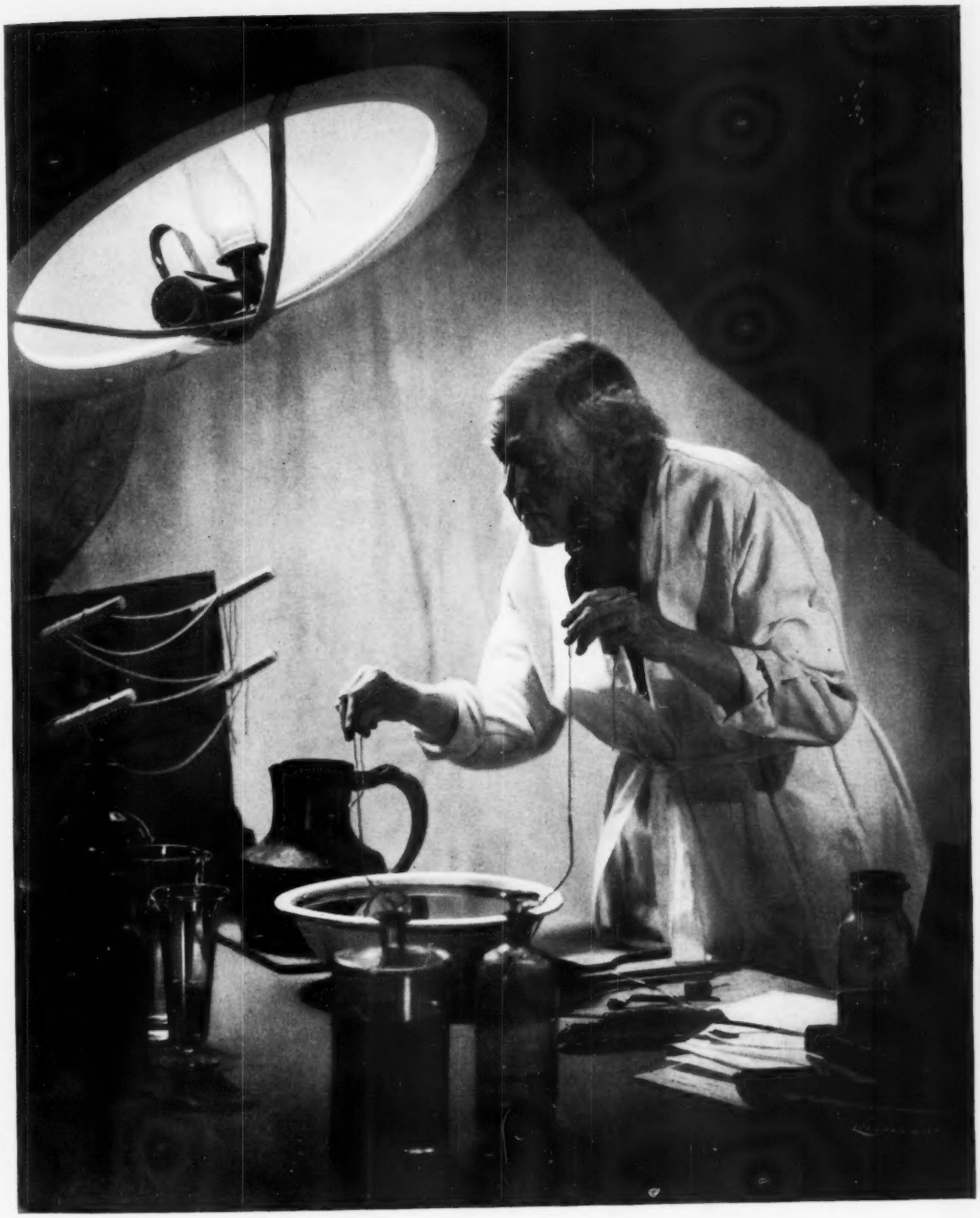

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SUTUREGRAM

NUMBER TEN IN A SERIES

Complications of Suturing (continued)

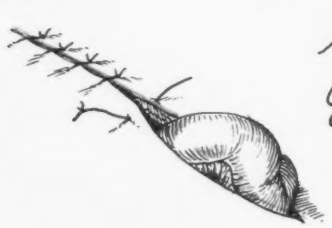
Evisceration

Wound develops sero-sanguinous discharge 5th to 9th day postoperatively.

Skin wound bulges over separated tissues beneath

If above signs are present remove one or two sutures and inspect beneath

Evisceration occurs after sutures are removed



SUTUREGRAM

NUMBER TEN (CONTINUED)

Causes of Evisceration

Insecure closure and Failure of Healing of peritoneum and posterior sheath.

1. Causes of Insecure Closure
   a. Tissues thin - sutures tear out easily
   b. Necrosis of tissues c. Unusual strain
   d. Sutures rapidly absorbed
   e. Knot becomes untied

2. Failure of Healing . . . .

Local Causes
- Inadequate blood supply
- Infection
- Interposition of omentum

General Causes
- Anemia
- Malignancy
- Low serum protein
- Low tissue - vitamin C

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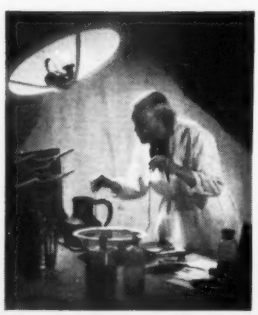

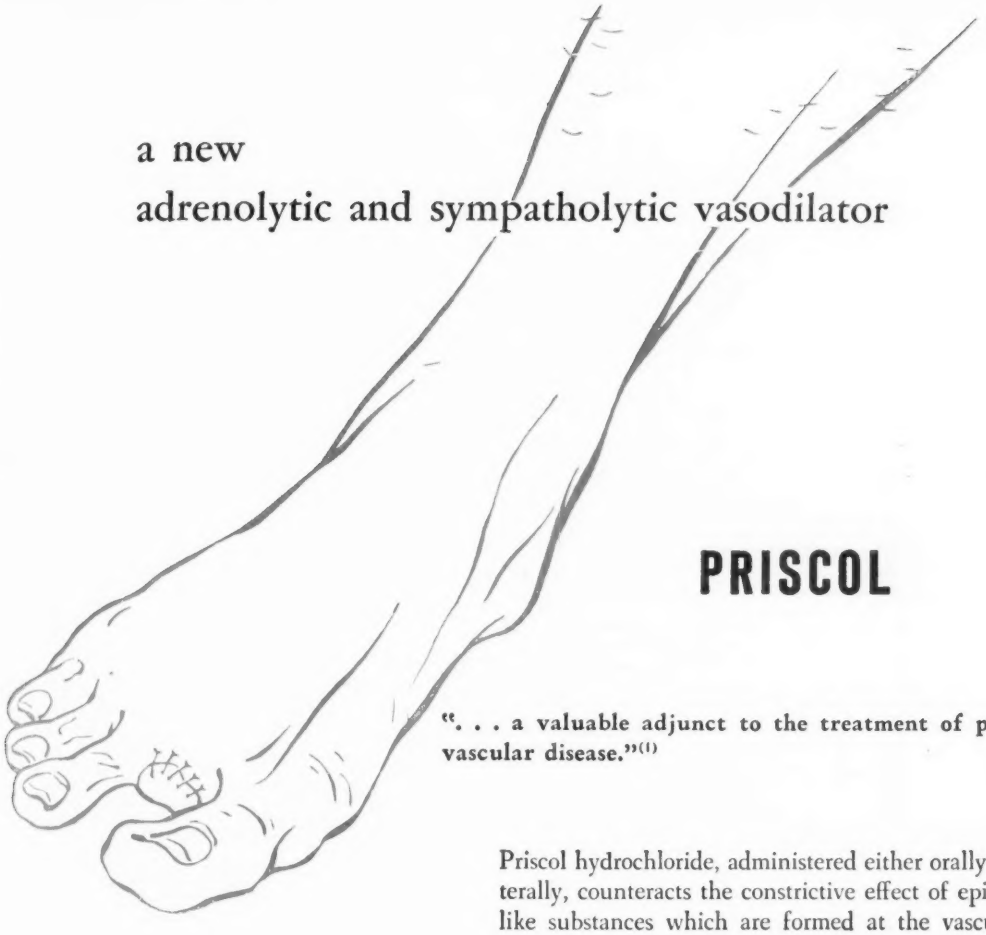

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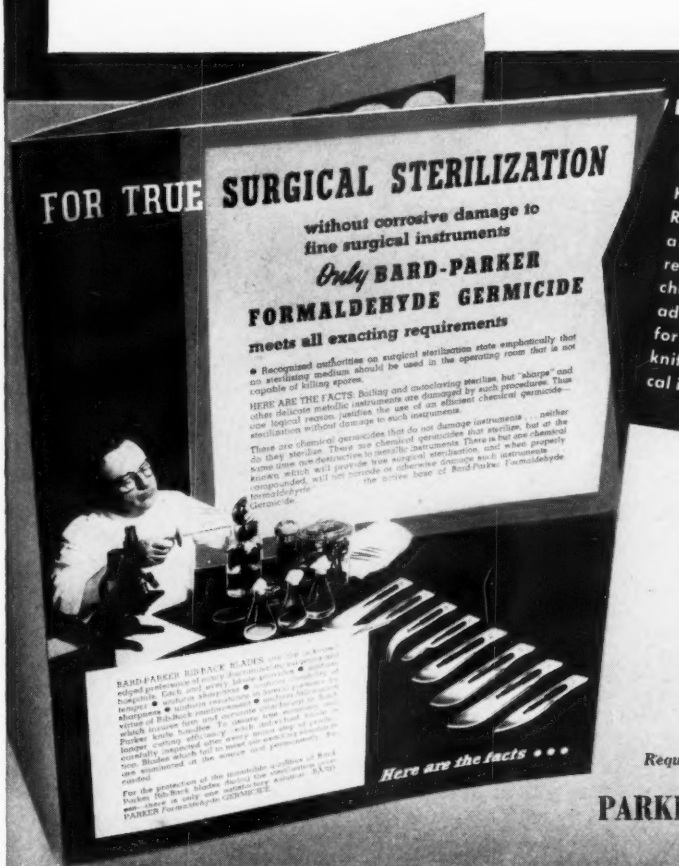
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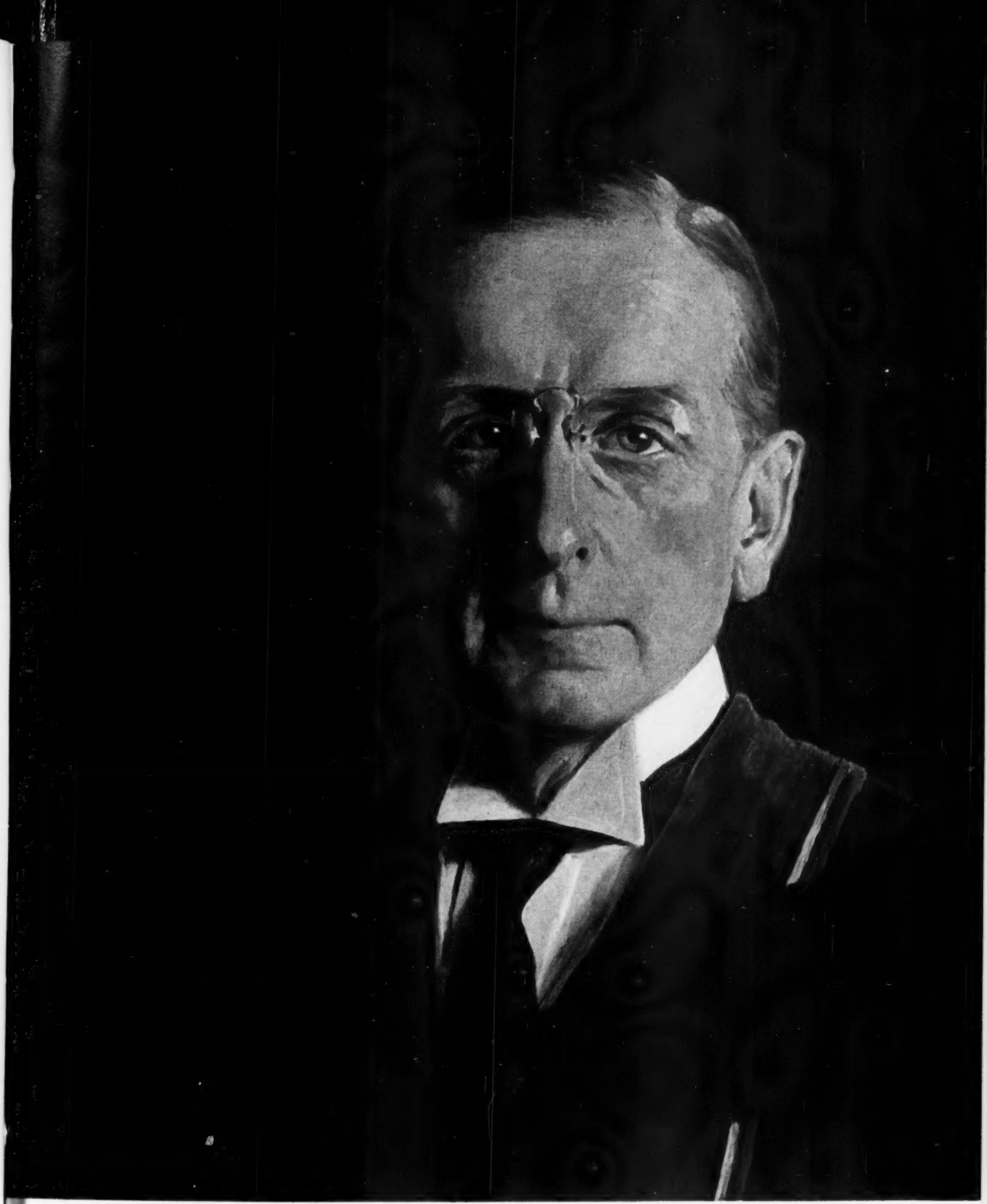

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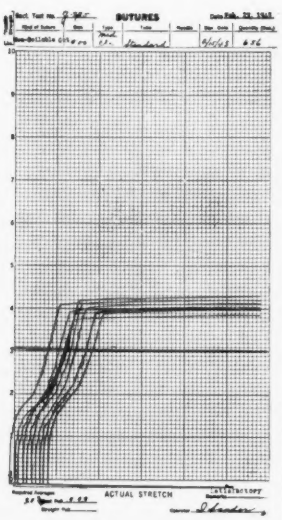

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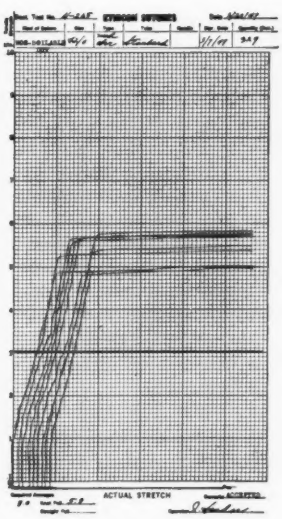

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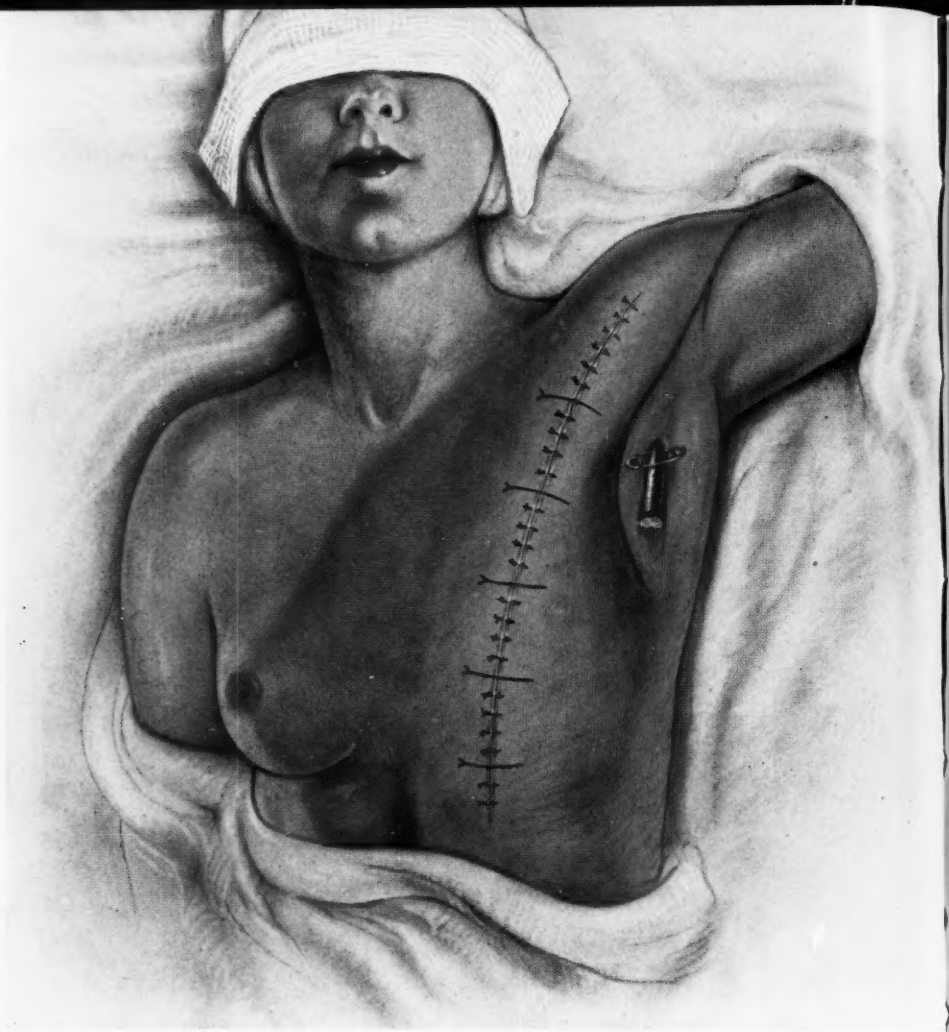

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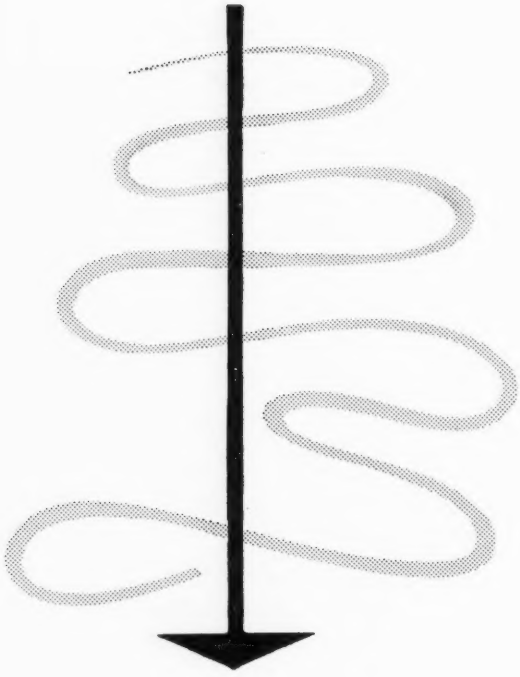

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Original Communications

THE PROBLEM OF THE SOLITARY LUNG TUMORS

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DURING the past decade the use of roentgenography has become more widespread than ever before. In particular, roentgen examination of the thorax in apparently normal individuals has become one of the major factors in preventive medicine. It is for this reason that the clinician is more frequently confronted with diagnostic chest problems in people who profess no subjective symptoms. During World War II every member of the Armed Forces had a roentgen examination of the thorax on induction into the service and again on separation from the service. In addition to this many thousands of young people throughout the country are subject to chest examinations before being accepted at universities or for employment. It is among these apparently normal, healthy people that the occasional solitary "shadow" or "spot" is discovered on an otherwise normal lung field. The diagnosis and the management of these asymptomatic lesions may constitute a very real problem since history and physical findings are frequently noncontributory. It seems apparent that the incidence of these particular diagnostic problems will not subside as there is every indication that the widespread use of roentgenography will continue. As more roentgenograms of the thorax are made in apparently healthy individuals, an increasing number of unsuspected lesions of the lung will be detected.

The clinical management of the apparently normal individual who has an undiagnosed solitary lesion in the lung is frequently difficult. In past years an accepted procedure in the management of these patients has been observation over varying periods of time. However, the value of clinical observation alone varies tremendously with the conscientiousness of the clinician and the fundamental intelligence and the cooperation of the patient. It is for these reasons that the fate of the majority of the "watched" tumors of the chest is unknown. We may assume that the majority of these lesions were probably benign, otherwise the patients would likely re-establish contact with their physicians.

In the past decade there has been continued improvement in surgical and anesthesia techniques and the problem of elective exploration of the thorax has

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been greatly simplified. Ten years ago a thoracotomy was looked upon in most communities as a hazardous procedure and the presence of a benign tumor did not justify such a heroic operation. At the present time, however, exploratory thoracotomy can be performed by competent personnel with an expected mortality rate of less than 1 per cent. Consequently, exploration of the thorax for the purpose of tissue biopsy or extirpation of a benign tumor is a commonplace, accepted procedure today.

As more chest surgery has been performed in recent years, we have had greater opportunity to confirm our clinical and roentgenologic diagnoses. The purpose of this paper is to present a representative series of cases that were observed over a period of eighteen months in the department of thoracic surgery at the Walter Reed General Hospital. These case histories have been carefully selected and are presented with one purpose in mind. It is our belief that accurate, preoperative diagnosis of an asymptomatic lung tumor is uncertain and, in most cases, impossible to make with the facilities that are generally available. Each of the twenty-four patients who are to be reported upon had a roentgen examination of the chest during a routine physical examination. In each case a round pulmonary lesion was discovered and in every case the lesion was completely asymptomatic. All of these patients were hospitalized for varying periods of time and thorough examinations were performed in an effort to make a concrete clinical diagnosis. No patient is included in this series who had an unexplained cough, fever, hemoptysis, chest pain, weight loss, or any localizing symptom that could be attributed to a primary or metastatic lung tumor. Each of these patients was hospitalized for an unrelated condition or because of the solitary lung tumor that had been discovered on an induction or a separation roentgenogram. The lesion under suspicion was in every case solitary and asymptomatic. Each of these patients was presented at The Tumor Board Conference or Thoracic Surgery Conference before operation. It is very interesting that there was never complete unanimity of opinion among the clinicians and radiologists who attended these conferences as to the specific diagnosis in each case. It is of more interest, however, that despite the wide variety of impressions which were proffered, all were considered benign tumors before operation. However, operation was advised to each of these twenty-four patients on the simple premise that diagnosis without tissue biopsy is only conjecture. All twenty-four patients agreed to surgical intervention and in each case a thoracotomy was performed. In this series of operative procedures both the mortality and the morbidity rates were zero. We feel that this group of patients is a representative one and that these findings should be presented to demonstrate the difficulty in establishing a diagnosis in the presence of solitary asymptomatic lung tumor without an actual tissue biopsy.

CASE HISTORIES

The inclusion of twenty-four case presentations in this discussion is not feasible, nor is it necessary. We have selected ten clinical abstracts and illustrations that are representative of the group. Although each case history has been condensed in the interest of brevity it is understood that each of these pa-

TABLE I. PERTINENT INFORMATION OF CASE HISTORIES INCLUDED IN THIS SERIES

CASE NO.	AGE YR.	PREOPERATIVE DIAGNOSIS	POSTOPERATIVE DIAGNOSIS	PROCEDURES	MORBIDITY	DATE
1	57	Tuberculoma	Tuberculoma	Wedge resection	0	12/ 3/45
2	51	Tuberculoma	Tuberculoma	Wedge resection	0	6/ 4/46
3	26	Tuberculoma	Tuberculoma	R.L.L. lobectomy	0	
4	51	Tuberculoma	Bronchiogenic carcinoma	L.L.L. lobectomy	0	8/ 2/46
5	47	Undetermined	Hamartoma	Wedge resection	0	7/ 4/45
6	51	Fibrous nodule	Metastatic adenocarcinoma	R.U.L. lobectomy	0	9/16/46
7	28	Bronchiogenic cyst	Lymphosarcoma	Excision	0	10/15/46
8	32	Bronchiogenic cyst	Bronchiogenic cyst	R.U.L. lobectomy	0	9 /8/46
9	24	Neurofibroma	Neurofibroma	Excision	0	5/ 5/46
10	36	Bronchiogenic cyst	Neurofibrosarcoma	1. Excision 2. Block excision of chest wall	0 0	7/10/46 7/21/46
11	26	Bronchiogenic cyst	Caseous lymph gland	Biopsy	0	10/16/45
12	36	Bronchiogenic cyst	Bronchiogenic cyst	Excision	0	9/12/44
13	27	Bronchiogenic cyst	Echinococcus cyst	R.U.L. lobectomy	0	5/ 8/45
14	27	Echinococcus cyst	Bronchiogenic cyst	Excision	0	11/ 8/44
15	44	Bronchiogenic cyst	Diaphragmatic hernia	Repair of diaphragm	0	3/28/47
16	31	Bronchiogenic cyst	Bronchiogenic cyst	R.M.L. lobectomy	0	4/ 8/47
17	19	Tuberculoma	Tuberculoma	Lingulectomy	0	5/20/47
18	52	Bronchiogenic carcinoma	Tuberculoma	Wedge resection	0	5/25/47
19	38	Undetermined	Diaphragmatic hernia, congenital	Repair	0	4/11/47
20	31	Bronchiogenic cyst	Bronchiogenic cyst	Excision	0	4/ 8/47
21	19	Undetermined	Cavernous hemangioma arising in mediastinum	Excision	0	4/ 9/47
22	57	Tuberculoma	Tuberculoma	Excision	0	1/ 8/47
23	19	Empyema	Bronchiogenic cyst	Excision	0	7/16/47
24	20	Undetermined	Tuberculosis	Lobectomy	0	10/ 7/47

tients received as complete a clinical study as the resources of a modern general hospital would permit. The majority of accepted diagnostic adjuncts have been employed prior to surgical exploration.

CASE 1.—A white patient, aged 57 years, was admitted to the Walter Reed General Hospital with a diagnosis of possible bladder neoplasm accompanied by a solitary lung metastasis. Complete genitourinary examination revealed a benign verruca of the bladder which was removed transurethrally. Roentgen examination revealed a round, solitary tumor in the basal division of the right lower lobe. After an uneventful postoperative recovery the patient returned to general duty. Final diagnosis was tuberculoma.

CASE 2.—A white patient, aged 51 years, was admitted to the Walter Reed General Hospital for treatment of hypertrophic arthritis of the lumbar spine. Routine roentgenographic examination of the chest revealed a solitary lesion in the left lower lobe that was not present on a roentgenogram made four years earlier. There were no symptoms attributable to a pulmonary lesion. The preoperative impression was benign tumor, probably tuberculoma. Exploratory thoracotomy was performed on June 4, 1946, and the tumor removed by wedge resection of the left lower lobe. The patient made an uneventful recovery following this operation and was discharged from the hospital. Final diagnosis was tuberculoma.

CASE 3.—A white patient, aged 26 years, was admitted to the Walter Reed General Hospital in November, 1944, as the dependent wife of an army officer. Roentgen examination revealed a round mass in the dorsal division of the right lower lobe. The tentative

impression of the attending physicians was tuberculoma and no treatment advised. Approximately one and one-half years later another roentgen examination of the chest was performed and there was a marked change in the character of the solitary lesion. During this period of observation the lesion had increased in size and showed definite central cavitation. The patient was transferred to a tuberculosis sanatorium and a right pneumothorax was instituted. The roentgen films were reviewed several months later and presented for the first time at the Thoracic Surgery Conference in the Walter Reed General Hospital. Excisional surgery was recommended and the patient returned to have a right lower lobe lobectomy performed. The patient has been discharged to her own care and is enjoying excellent health one year after operation. Final diagnosis was tuberculoma.

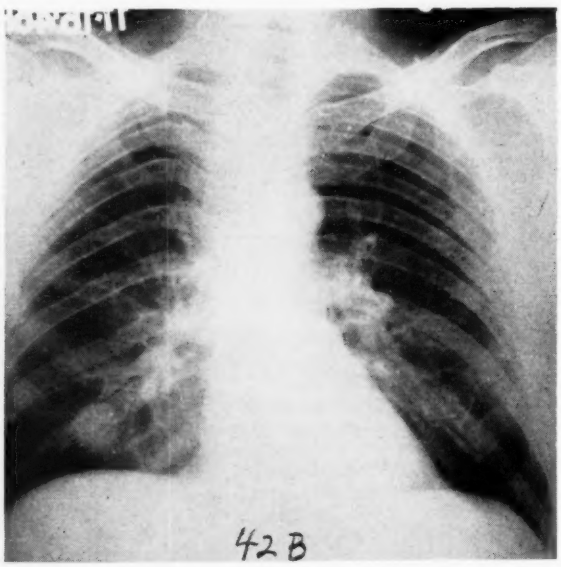

Fig. 1 (Case 1).—The tumor is located in the basal portion of the right lower lobe. The clinical impression of tuberculoma was confirmed by surgical removal.

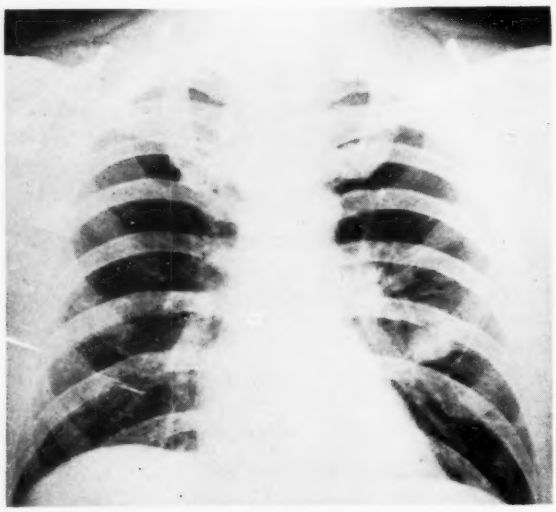

Fig. 2 (Case 2).—Asymptomatic tumor in the left lower lobe; final diagnosis was tuberculoma.

CASE 4.—A white patient, aged 51 years, was transferred to the Walter Reed General Hospital for study of an undiagnosed lung tumor. The solitary lesion was demonstrated on a routine roentgen examination. There were no additional subjective or objective findings. The tumor was localized to the left lower lobe and was thought to be tuberculoma. On Aug. 2, 1946, a thoracotomy was performed and the lesion removed by a left lower lobe

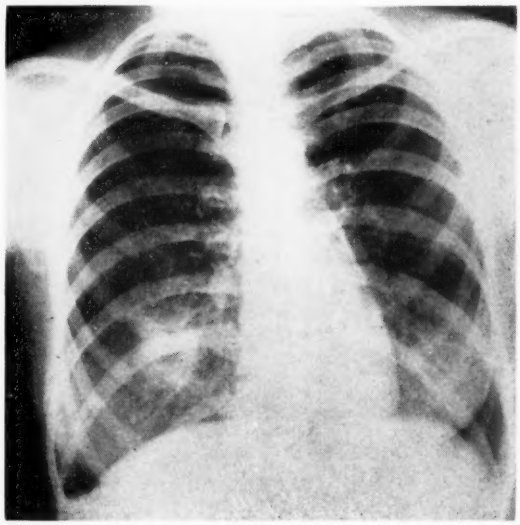

Fig. 3 (Case 3).—Note central cavitation and fluid level in tumor of right lower lobe. This tuberculoma had been under observation for two years prior to lobectomy.

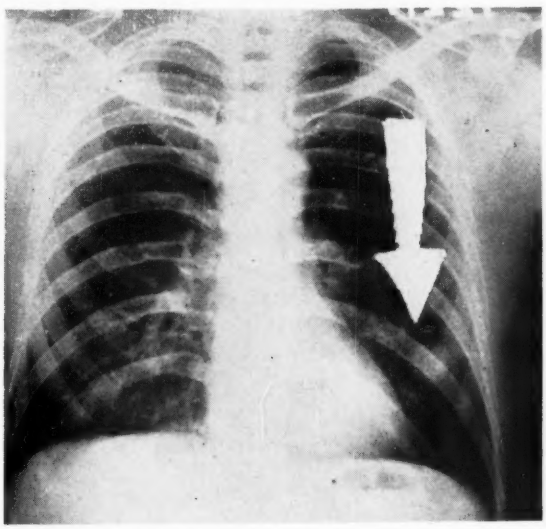

Fig. 4 (Case 4).—Tumor of left lower lobe which proved to be a peripheral bronchiogenic carcinoma. The clinical impression before operation was tuberculoma. There was no evidence of metastasis eighteen months after lobectomy.

lobectomy. After an uneventful recovery the officer returned to general duty. The patient was last seen eighteen months after operation and appeared to be in excellent health. Final diagnosis was bronchiogenic carcinoma.

CASE 5.—A Negro patient, aged 47 years, was inducted into the Army in August, 1942. Past history revealed a primary syphilitic lesion in 1929 that was inadequately

treated by arsenicals and bismuth. While on overseas duty in May, 1944, the patient was hospitalized because of papular eruption of both palmar surfaces and an associated sore throat. Serologic examination was reported as strongly positive and antisyphilitic therapy was instituted. Complete examination at this time was entirely normal except for the roentgen evidence of a round tumor in the right middle lobe. The impression of pulmonary gumma was entertained but the lesion showed no regression or change under treatment. The complete examination at the Walter Reed General Hospital confirmed the finding of the lung tumor but no specific diagnosis could be made. On July 4, 1945, the right thoracic cavity was explored and the tumor removed from the right middle lobe. The patient made an uneventful recovery and returned to duty. Final diagnosis was hamartoma.

Fig. 5 (Case 5).—Lateral projection reveals solitary tumor in right middle lobe. Microscopic diagnosis following middle lobe lobectomy was hamartoma.

CASE 6.—A white, patient, aged 51 years, was operated upon in November, 1944, at which time an annular lesion of the sigmoid colon was resected and an end-to-end anastomosis of the bowel performed. The tumor was registered with the diagnosis of adenocarcinoma, with no regional metastasis. The officer returned to duty and for a period of two years enjoyed excellent health. He returned upon order of the Surgeon General for re-evaluation in April, 1946. A complete examination revealed normal findings at this time except for the roentgenogram, which revealed a small area of increased density in the right upper lung field. A review of the old x-ray films proved that the lesion was not present in 1944. Six months of observation was recommended during which time there was no apparent change in the roentgenogram and the officer continued in good health. At the recommendation of the Thoracic Surgery Conference an exploratory thoracotomy was performed on Sept. 16, 1946. The lesion was easily removed from the right upper lobe and frozen section examination revealed the nodule as adenocarcinoma, metastatic from the large bowel. A right upper lobe lobectomy was then performed. There was no evidence of other metastasis in the right lung or mediastinum. The immediate postoperative course was uneventful and the patient returned to limited service. Final diagnosis was adenocarcinoma, metastatic from the large bowel.

CASE 7.—A white patient, aged 28 years, was taken ill and hospitalized with the diagnosis of pneumonia while on overseas duty. Roentgen examination revealed a shadow characteristic of pneumonitis which gradually resolved. Following resolution of the alleged pneumonic process another abnormal shadow was discovered. This lesion was very well demar-

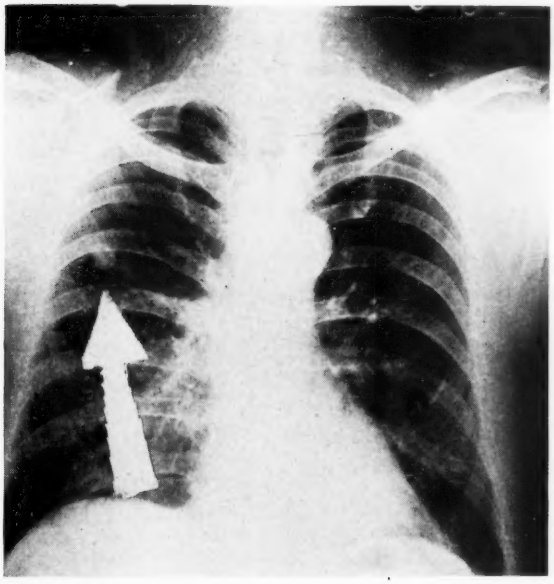

Fig. 6 (Case 6).—Roentgenogram appears normal except for solitary lesion of right upper lobe. Microscopic diagnosis following right upper lobe lobectomy was adenocarcinoma, metastatic from large bowel. The patient was in good health fifteen months after surgery.

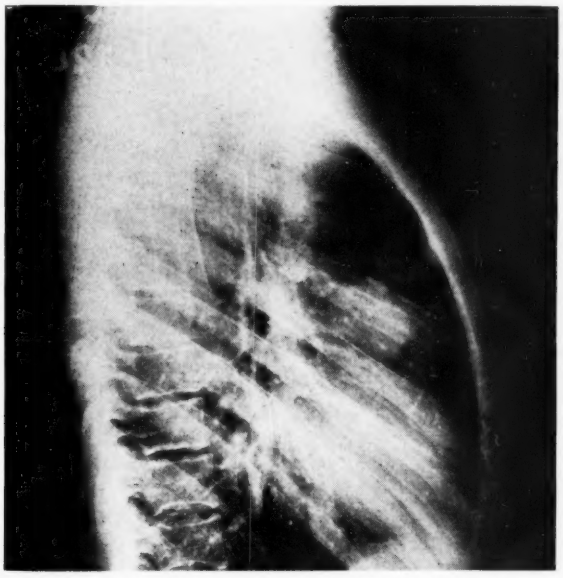

Fig. 7 (Case 7).—Lateral projection of thorax reveals solitary lesion which was presumed to be in the right upper lobe. The tumor was removed surgically and the pathologic diagnosis of lymphosarcoma established. This tumor was extrapulmonary, apparently arising from the mediastinum.

cated and bore no resemblance to the original process. After five months of observation the lesion showed no significant change although the patient was entirely free of symptoms. After the patient was transferred to the Walter Reed General Hospital physical examination was entirely normal except for the lesion which could be radiologically demonstrated in the right upper lobe. It was felt that this patient had a bronchiogenic cyst that had probably become infected and produced a superimposed pneumonitis. Exploratory thoracotomy in October, 1946, revealed an extrapulmonary solid tumor that probably arose from mediastinum. This soldier made an uneventful recovery and has enjoyed excellent health since time of discharge one year ago. Final diagnosis was lymphosarcoma.

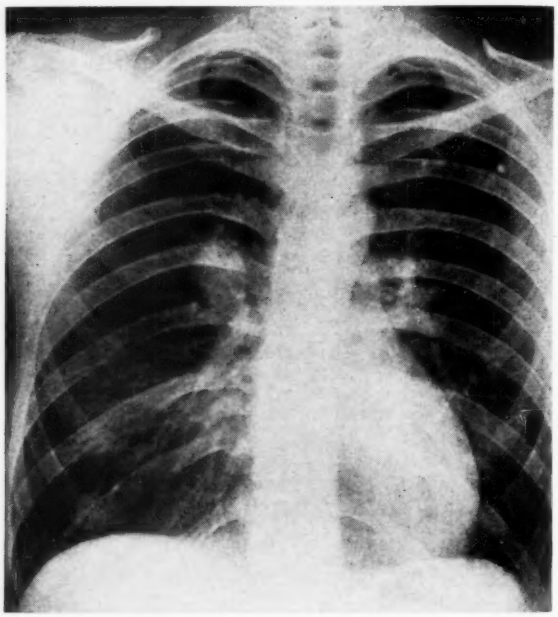

Fig. 8 (Case 8).—Routine Army Separation roentgenogram of the chest revealing an asymptomatic tumor in the right upper lobe. Postoperative diagnosis was bronchiogenic cyst.

Case 8.—A white patient, aged 32 years, was transferred from a separation center to the Walter Reed General Hospital. Final type physical examination was entirely normal except for the roentgen finding of a solitary lung tumor. The lesion was located in the right upper lobe and was thought to be a bronchiogenic cyst. Exploratory thoracotomy was performed and it was necessary to perform a right upper lobe lobectomy. Recovery was prompt and the patient was discharged from the hospital approximately one month after operation. Final diagnosis was bronchiogenic cyst.

Case 10.—A white patient, aged 36 years, had roentgen evidence of intrathoracic tumor detected at an Army Separation Center. The lesion appeared to be perfectly spherical and was about the size of a tennis ball. A review of the induction roentgenogram showed no evidence of the lesion. It was generally agreed by the members of the Tumor Board that the neoplasm was probably benign and represented a bronchiogenic cyst arising from the posterolateral segment of the left upper lobe. An exploratory thoracotomy was performed on July 10, 1946, and lesion was arising from the chest wall and proved to be entirely extrapulmonary. Microscopic studies subsequently yielded the diagnosis of neurofibrosarcoma with microscopic capsular invasion. A second operation was then performed and a block excision of the chest wall performed. The patient withstood both operative procedures very well and has been discharged from the service. Final diagnosis was neurofibrosarcoma.

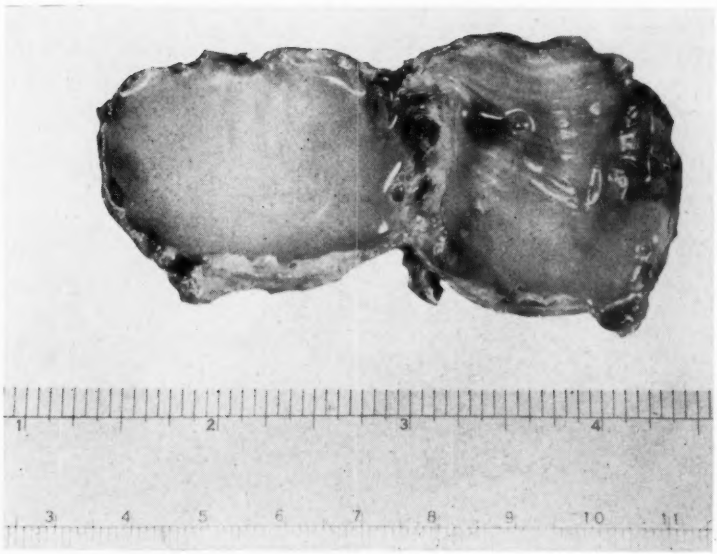

Fig. 9 (Case 8).—Cross section of bronchiogenic cyst removed during exploratory thoracotomy.

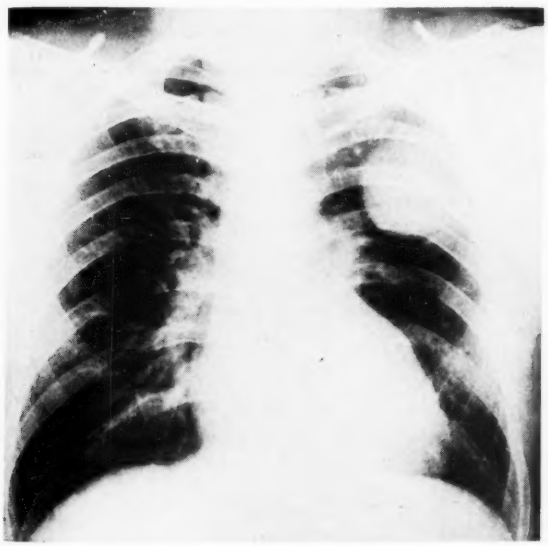

Fig. 10 (Case 9).—Neurofibrosarcoma of the chest wall discovered on routine Army Separation film. This tumor moved with respiration and was thought to be intrapulmonary.

CASE 13.—A white patient, aged 27 years, was hospitalized while on active duty within the continental limits of the United States. The chief complaint was acute sore throat. The patient rapidly recovered but further studies were ordered after a routine admission roentgenogram revealed a large circumscribed lesion in the right upper lobe. All physical findings were normal; however, the Kahn and Wassermann tests were reported as strongly positive. There were no symptoms of any kind; past history revealed that the

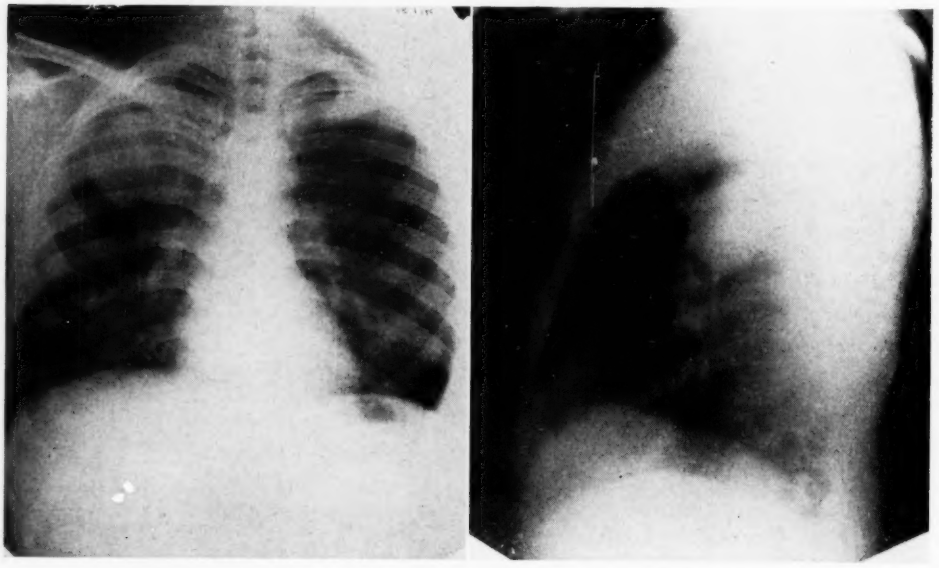

Fig. 11. Fig. 12.

Fig. 11 (Case 10).—Echinococcus cyst in right upper lobe discovered on a routine hospital admission roentgenogram of chest.

Fig. 12 (Case 10).—Lateral view of echinococcus cyst in right upper lobe.

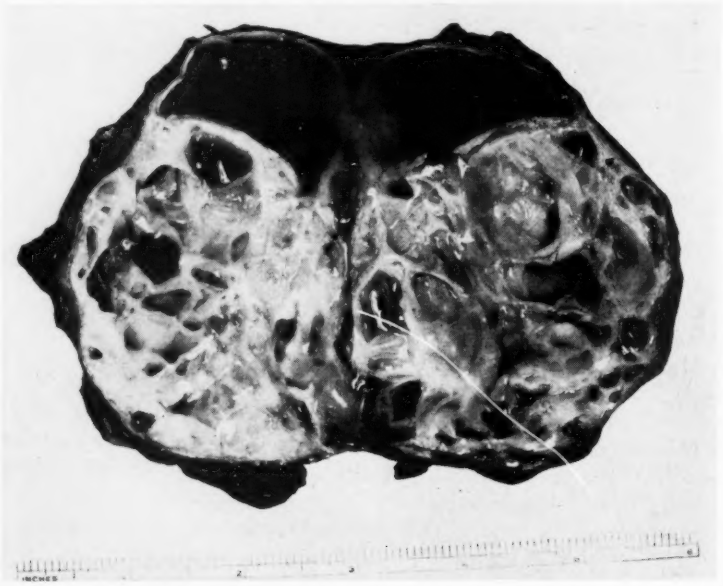

Fig. 13 (Case 20).—Cross section of bronchiogenic cyst removed during thoracotomy.

soldier had several years in England, North Africa, and Sicily. In May, 1945, a right upper lobe lobectomy was performed and the lesion identified as an echinococcus cyst. Recovery was complete and uneventful. Final diagnosis was echinococcus cyst.

COMMENT

Twenty-four case presentations do not constitute an impressive series of intrathoracic tumors. However, it must be emphasized that each of these cases has been selected from a much greater number because it conforms to these specific criteria:

1. The lesion was an incidental radiologic discovery.
2. The impression of a solitary lung tumor was based on the roentgen findings alone.
3. There were no symptoms or physical findings related to the tumor.
4. All lesions were considered benign neoplasms preoperatively.

Patients who had obvious chest wall or mediastinal tumors are excluded from this series. Likewise, no case is included in which the patient had a tumor amenable to bronchoscopic biopsy.

After a comprehensive study of the pulmonary tumors removed surgically at the Walter Reed General Hospital it was our opinion that ultimately tissue biopsy is the only diagnostic procedure of true value. Since most of the patients with pulmonary neoplasms have some symptoms of thoracic disease there is little question that surgical intervention is indicated in the majority of cases. Few conscientious clinicians would hesitate to ask for surgical opinion when a patient with complaints of cough, sputum, hemoptysis, fever, weight loss, and the like has roentgen evidence of a lung tumor. However, many doctors are reluctant to consider the patient with an asymptomatic lung tumor as a candidate for surgery. The belief that solitary, round masses in the lung fields are relatively harmless entities is unfortunately a widespread medical opinion. The series of case histories presented in this paper demonstrates well the difficulty of establishing a diagnosis without tissue biopsy; this is particularly significant since the diagnostic facilities at hand were unlimited. It is of particular note that approximately 15 per cent of the tumors proved to be malignant neoplasms after adequate tissue studies were performed. This in itself justifies surgical exploration of every solitary tumor of the lung even though the patient is symptom-free and the lesion has every indication of being benign.

A review of the cases presented (see Table I) discloses that seven of the tumors proved to be tuberculomas. Of the remaining seventeen, four lesions were malignant tumors. Again it is unfortunate that most doctors consider a tuberculoma as an innocuous lesion if it is not accompanied with roentgen evidence of active parenchymal disease. Case 3 (see Figs. 1 and 4) illustrates one of the complications that may follow in an untreated patient. This tumor was observed for a period of almost two years while it progressed to central cavitation whereupon the patient's sputum demonstrated acid-fast bacilli for the first time. The opinion that all tuberculomas should be excised is generally accepted by thoracic surgeons today. Experience has shown that the tuberculoma is

benign only in the sense that it does not undergo neoplastic degeneration; the benignity of the lesion ceases there.

It must also be pointed out that the age incidence of the patients presented in this series is comparatively young. Since these people were seen in a military hospital during wartime the reason is self-evident. A comparable series in which the average patient age exceeded 50 years would probably show a higher incidence of malignant tumors, thereby emphasizing even more the importance of surgical exploration in the presence of an asymptomatic lung tumor.

CONCLUSIONS

With the continued increase in radiologic methods of diagnosis we can expect to see a greater incidence of asymptomatic intrathoracic neoplasms. The question will always arise in the mind of the clinician, is this tumor benign or malignant? From the experience gained in this series of twenty-four cases we can assume the question can be answered only by tissue study of the entire lesion. Prolonged observation is always inconclusive and may prove disastrous in certain instances. Accurate diagnosis in any tumor depends on tissue study, and intrathoracic neoplasms are no exception. With the continued refinement of surgical and anesthetic techniques the procedure of exploratory thoracotomy has become an accepted one in all age groups. For this reason alone there seems to be little justification in overlooking the only certain method of diagnosis and treatment in the management of the solitary, asymptomatic lung tumor.

SUMMARY

A series of twenty-four case histories is presented. All of the patients were operated upon because of roentgen evidence of a solitary lung tumor.

The mortality rate was zero; one patient developed a partial hemothorax necessitating a partial decortication.

Four of the tumors proved to be malignant; seven were diagnosed as tuberculomas.

CARCINOMA OF THE SUPERIOR MEDIASTINAL SEGMENT OF THE ESOPHAGUS

A Technique for Resection With Restoration of Continuity of the Alimentary Canal

Richard H. Sweet, M.D., Boston, Mass.

IT WAS suggested in 1942 that from the standpoint of surgical management of cases of carcinoma it is convenient to divide the thoracic portion of the esophagus into *fourths.*[1] The upper fourth, or superior mediastinal segment, extends from the base of the neck to the superior margin of the aortic arch; the middle two fourths from the superior margin of the aortic arch to the level of the inferior pulmonary veins, and the lower fourth from that point to the diaphragm. At the time when this subdivision into segments was proposed, a satisfactory technique for the extirpation of carcinoma of the esophagus was available only in the case of a growth situated in the lower portion. This is the operation of partial esophagectomy and gastrectomy with a low intrathoracic esophagogastric anastomosis. For lesions in the middle half, the Torek operation was still in use. In a short time, however, the operation of partial esophagectomy and primary esophagogastrostomy was modified to include such cases and the Torek operation was abandoned.[2, 3, 4]

For the removal of a lesion located in the upper fourth of the thoracic portion of the esophagus, on the other hand, no satisfactory technique has been developed up to the present time. A carcinoma in this segment is too low for the use of the Wookey operation,[5] which is applicable only in cases where the growth lies in the cervical region. It is too high for the performance of a supra-aortic intrathoracic esophagogastric anastomosis. It is unsuitable, furthermore, for the application of the Torek operation because of the fact that if the esophagus is divided high enough to avoid the upper margin of the tumor, the proximal portion is too short to make a satisfactory cervical esophagostomy. Recently a modification of the technique used for the removal of tumors in the midthoracic segment of the esophagus has been developed so that now a growth situated in the superior mediastinal segment can be resected and a primary esophagogastric anastomosis made in the neck using the short proximal esophageal stump.

THE TECHNICAL PROBLEM

That the stomach can be mobilized sufficiently to make it possible to place the fundus in the apex of the left pleural cavity has been obvious for several years. This fact was discovered as a result of the adaptation of the operation of partial esophagectomy with primary intrathoracic esophagogastrostomy to the removal of carcinoma high in the midthoracic region. In the case of carcinoma in the superior mediastinal segment of the esophagus it is impossible from within

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the thoracic cavity to reach beyond the proximal border of the growth for division of the esophagus. A separate cervical incision must therefore be used for that purpose. The problem then arises as to how to bring the fundus of the previously mobilized stomach from the apex of the left pleural cavity into the neck where the esophagogastric anastomosis must be made.

The space through which the esophagus normally passes from the neck into the superior mediastinum is not large enough to accommodate the fundus of the stomach. Furthermore, even if the fundus could be forced through this narrow passageway between the trachea and the spine, there would not be room enough to perform a satisfactory anastomosis in the space available between the spine, the trachea, and the carotid sheath. As a second alternative, the fundus might be brought out through a short anterior incision in the second intercostal space and then up into the neck through a subcutaneous tunnel. The obvious objection to this possibility is that the pressure of the overlying skin, fascia, and muscle would cause too much compression of the stomach and the anastomosis against the underlying structures. Ample room can be obtained, however, by resecting the inner one-half of the clavicle and a comparable segment of the first rib so that the fundus can be passed into the neck without pressure or constriction to meet the short, high-lying proximal esophageal segment. This technique was developed to overcome the difficulty of restoring the continuity of the alimentary canal in a patient with congenital atresia of the esophagus who had been treated by closure of the tracheoesophageal fistula and the establishment of a cervical esophagostomy and a gastrostomy instead of by primary anastomosis. This case has been reported elsewhere.[6]

DESCRIPTION OF THE OPERATION

The operation is performed in one stage as follows:

(1) *First Step of the Procedure—Dissection of the Esophagus and Mobilization of the Stomach.*—The patient is placed on the right side with the left arm held forward, the hand in front of the face. A long oblique incision is made along the course of the eighth rib from the costal margin in front to within a few centimeters of the midline in back, where it is made to curve upward between the spine and the scapula a short distance. The eighth rib is resected, cutting its neck posteriorly and the cartilage anteriorly. A rib spreader is inserted. If sufficient exposure is not available to reach the superior mediastinum, the seventh, sixth, and sometimes the fifth ribs may be divided posteriorly. The dissection is begun in the region of the tumor after incising the mediastinal pleura above the aortic arch behind the left subclavian artery. If the tumor-bearing portion of the esophagus can be freed sufficiently to make it possible to perform a resection, the operation is continued by completing the dissection of the entire length of the esophagus within the thorax. The freeing of the upper fourth presents no particular problem except that the thoracic duct must be identified as it crosses the esophagus just above the aortic arch. If the duct is invaded by tumor or is too adherent to be dissected free, or if it has been injured during the dissection, it must be ligated to prevent the development of a chylous hydrothorax after operation.[4] Below the aortic arch the esophageal arteries must be

tied and cut. These arise from the aortic arch, the bronchial arteries, and the descending aorta. In freeing the lower portion of the esophagus the periesophageal lymph nodes must be included in the dissection in so far as possible. After the entire thoracic portion of the esophagus has been dissected free, the phrenic nerve is crushed and the diaphragm is incised from a point close to its costal insertion through the margin of the esophageal hiatus. This permits the mobilization of the stomach which is begun by dividing the attachments of the fundus, including the gastrolienal ligament, the vasa brevia, and the left gastroepiploic vessels. The entire gastrocolic ligament is then incised all the way to the level of the pylorus, pains being taken to avoid injury to the anastomotic arcade of vessels along the greater curvature of the stomach through which a flow of blood is maintained by the right gastroepiploic artery. The left gastric vessels are tied and cut. The gastrohepatic ligament is incised as far as the level of the pylorus. Here, likewise, the integrity of the vascular arches along the lesser curvature which are supplied by the right gastric artery must be preserved. It is important to mention in this connection that the left gastric artery should be tied and cut close to its origin from the celiac axis to preserve its peripheral branches which form the greater portion of the vascular arcade along the lesser curvature.

After the mobilization of the stomach has been completed, the esophagus is cut across just above the cardia and the stump on the gastric side is inverted with a purse-string suture reinforced with a layer of Lembert sutures of silk. A piece of rubber tissue is tied over the proximal end and the esophagus is then pulled up and out from behind the aortic arch so as to make its later withdrawal into the neck somewhat easier.

The completely mobilized stomach is then drawn up into the left thoracic cavity behind the hilum of the lung and lateral to the aortic arch. Fixation in this location is maintained by means of a series of interrupted silk sutures between the gastric wall and the mediastinal pleural surface which overlies the descending aorta. The fundus of the stomach is allowed to be free in the superior portion of the pleural cavity until the cervical portion of the operation is performed. The fixation sutures already applied prevent its falling down out of reach after the chest has been closed. The diaphragm is sutured to the stomach just above the pylorus and the remainder of the diaphragmatic incision is closed.

A Foley catheter is led out through a small stab incision in the tenth intercostal space posteriorly. To complete the first stage of the operation the lung is expanded by the anesthetist and the thoracotomy incision is closed using interrupted silk sutures in all layers.

(2) *Second Step of the Procedure—Performance of the Intracervical Esophagogastric Anastomosis.*—After closure of the thoracotomy incision has been completed, the patient is turned on his back and an incision is made along the anterior margin of the left sternocleidomastoid muscle to the suprasternal notch and then downward over the upper portion of the sternum to the level of the second costal cartilage. The pectoralis major muscle is incised close to its sternal attachment and reflected laterally, at the same time severing its insertion

in the medial portion of the clavicle. The sternal and medial clavicular insertions of the sternocleidomastoid muscle are severed and retracted laterally. The dissection is then deepened in the space between the carotid sheath and the trachea to expose the esophagus. By grasping it with a forceps the esophagus is pulled up from the mediastinum and out in front of the carotid sheath.

The medial half of the clavicle and a corresponding segment of the left first rib and costal cartilage are resected extraperiosteally. The clavicle should be cut with the Gigli saw. This produces a large opening from the base of the neck behind the lower end of the sternomastoid muscle into the apex of the left pleural cavity, through which the fundus of the stomach can be drawn easily and without danger of compression. The esophagus is pulled up from the mediastinum and out in front of the carotid sheath. The fundus is then brought forward medial to the apex of the lung and pulled up into the lower portion of the neck (Fig. 1). A short incision is made in the posterior wall of the fundus close to its apex and an anastomosis consisting of three layers of interrupted fine silk (00000) sutures is made. A careful approximation of mucosa-to-mucosa and muscle edge-to-muscle edge constitute the inner and middle layers. The outer layer is of mattress sutures. Several sutures are used to fix the fundus to the surrounding tissues of the neck to prevent tension on the anastomosis which, after its completion, lies in front of the carotid and internal jugular vessels (Fig. 2). The wound is closed by suturing the lower end of the sternocleidomastoid muscle and the medial cut edge of the pectoralis major muscle to the sternum and placing a layer of fine silk sutures in the subcutaneous fat and another in the skin. The wound is not drained.

CASE REPORT

As an illustration of the utilization of this operation in the management of carcinoma of the superior mediastinal segment of the esophagus, the following case report is submitted.

J. S., a white man, aged 55 years, entered the Baker Memorial unit of the Massachusetts General Hospital on Oct. 22, 1947. About three months previously he had noticed a certain amount of difficulty with swallowing when he choked on a piece of beefsteak. This did not occur again for a considerable period of time, but a few weeks before admission he had begun to notice difficulty in swallowing other foods, particularly bread. Following that time the dysphagia became increasingly noticeable so that he had to be very careful about what he ate although he was able to eat a fairly liberal diet. He had not lost much weight or strength and was still able to carry on with his work. He had never been ill in his life before this episode.

Roentgen-ray examination at a local hospital showed a lesion in the retrosternal region behind the manubrium of the sternum and he was therefore referred to the Baker Memorial for consideration of resection of the esophagus.

Physical examination revealed a man apparently in an excellent state of health. Blood pressure was slightly elevated, 160/100, but the heart sounds were normal. No murmurs could be heard.

Laboratory studies revealed a white blood count of 7,200 and a hemoglobin of 15.8 Gm. per cent. There were 88 polymorphonuclear cells, 10 small lymphocytes, and 2 monocytes. The stained specimen showed normal red blood cells and platelets with a rare polymorphonuclear cell showing toxic granules. The serum protein was 5.8 Gm. per cent, the

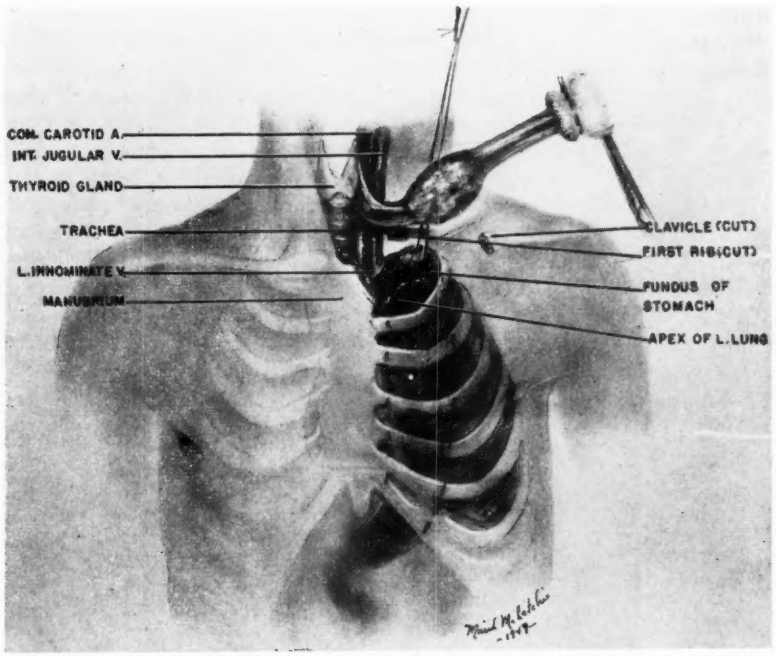

Fig. 1.—Drawing to illustrate the method of bringing the fundus of the stomach from the apex of the left pleural cavity into the neck through an opening produced by resecting the medial half of the clavicle and of the first rib.

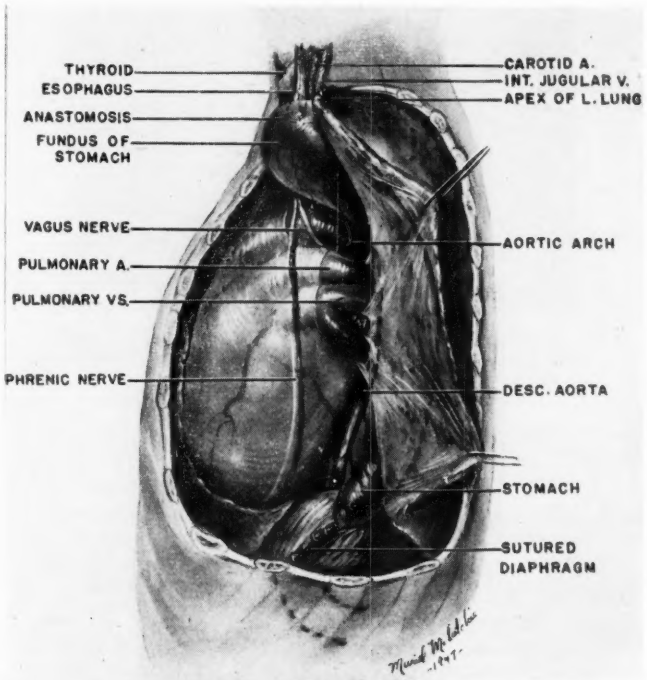

Fig. 2.—Drawing to show the relations of the stomach to the thoracic viscera and the structures in the base of the neck. Note: (1) The stomach passes behind the hilum of the lung and extends forward in the apex of the left pleural cavity medial to the lung. (2) At the completion of the operation the anastomosis is on the posterior surface of the fundus of the stomach and lies anterior to the carotid artery and jugular vein.

nonprotein nitrogen 22 mg. per cent, and the chloride 102 mg. per cent. The prothrombin time was 17 (normal, 18) seconds, and the fasting blood sugar 117 mg. per cent. Electrocardiogram showed no abnormality of the heart.

Roentgen-ray examination of the upper gastrointestinal tract showed a semiannular, nonobstructing carcinoma of the upper esophagus. There was an area of rigidity in the upper esophagus extending for about 6 cm. opposite the third, fourth, and fifth dorsal vertebrae, from approximately the level of the clavicles to the midportion of the aortic arch. There was no evidence of obstruction, but the esophagus was somewhat narrowed in this area, irregular in appearance, and showed definite destruction of the greater portion of the mucosa with a definite shelflike edge at the upper margin of the lesion (Fig. 3). The remainder of the esophagus appeared normal. The stomach, duodenum, and upper small intestine as far as outlined also appeared normal.

Roentgen-ray examination of the chest showed the lungs to be clear with no demonstrable evidence of metastasis or other pulmonary pathology. The heart was normal in size, shape, and position. There was no evidence of pleural effusion or other abnormality.

Fig. 3.—Case J. S. Preoperative roentgenogram showing the filling defect produced by the epidermoid carcinoma of the superior mediastinal segment of the esophagus at the level of the manubrium of the sternum.

After five days of preliminary preparation the patient was operated upon Oct. 28, 1947. A long oblique incision was made across the left side of the chest and the eighth rib was resected. A rib spreader was inserted and a good exposure of the entire mediastinum was obtained. An incision was made in the mediastinal pleura above the aortic arch and the esophagus was identified. The tumor lay well above the level of the aortic arch and its proximal extent actually passed up into the base of the neck. There was considerable periesophageal inflammatory thickening which made the dissection difficult, especially between the esophagus and the trachea. During this dissection the thoracic duct was identified. A strand of heavy silk was passed around it to facilitate its retraction. The duct was not injured in the course of the procedure and therefore it was not ligated.

When it became apparent that the growth could be dissected free, the dissection was carried down behind the aortic arch and an incision was made in the pleura below the arch all the way to the diaphragm. The esophagus was freed from the arch to the dia-

phragm. The diaphragm was then incised. There were no evidences of metastases within the abdomen, but there was a lymph node along the lower portion of the esophagus just below the diaphragm which seemed to be invaded by tumor. The liver was free from palpable nodules.

The stomach was not large, but it was readily mobilized. An extensive mobilization was performed dividing all of the vessels except the right gastric and the right gastro-epiploic arteries and veins and severing the gastrohepatic and gastrocolic ligaments as far as possible to the right. A heavy tie of silk was placed around the esophagus just above the cardia and the esophagus was cut across with a knife. The proximal end was covered with a piece of rubber tissue tied on and the distal end was inverted with a silk purse-string suture. This was reinforced with several interrupted Lembert sutures of fine silk. The esophagus was then pulled up from behind the aortic arch.

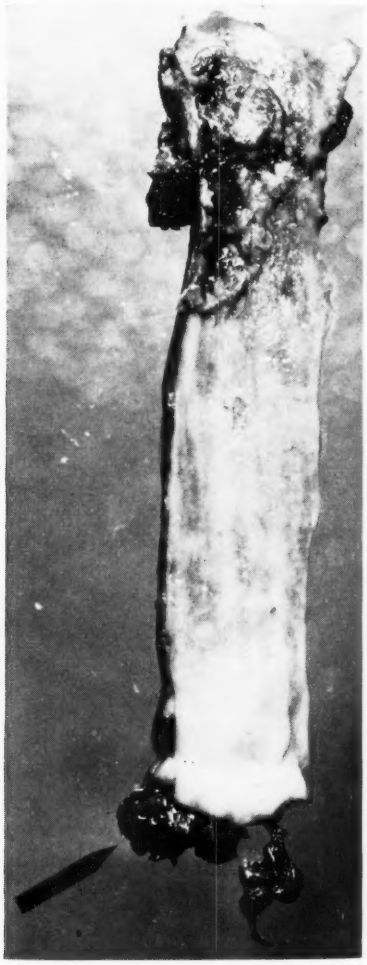

Fig. 4.—Case J. S. Photograph of the specimen after esophagectomy showing the primary tumor at the upper end of the esophagus and the lymph node at the lower end which was found to contain a metastasis (arrow).

The dissection was carried as far as possible up into the neck behind the carotid and subclavian vessels. The stomach was then drawn up into the chest to a point as high as possible and it was obvious that it could easily be pulled from beyond the apex of the chest into the neck, although there was not actually room enough to bring the fundus up behind the clavicle and first rib. The diaphragm was closed around the stomach just above the pylorus and the stomach itself was held in the thorax by means of a series

Fig. 5.—Case J. S. Postoperative roentgenograms showing anteroposterior view of the chest and base of the neck after the ingestion of barium. The fundus of the stomach and the anastomosis are seen lying above the level of the suprasternal notch.

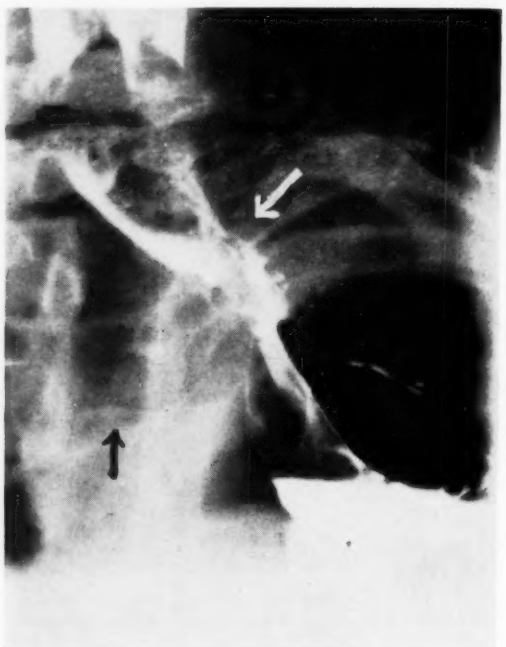

Fig. 6.—Case J. S. Postoperative roentgenogram centered over the cervical region. The white arrow points to the intracervical esophagogastric anastomosis. The black arrow indicates the suprasternal notch. The cut end of the remaining portion of the first rib can be seen. Note the exceedingly short length of esophagus above the anastomosis.

of sutures between the mediastinal pleura overlying the descending aorta and the posterior gastric wall. The lung was then expanded and the chest wall was closed using interrupted silk sutures. A Foley catheter was brought out through one of the lower interspaces. Streptomycin and penicillin solution was injected both above and below the diaphragm.

The patient was then turned on the back and an oblique incision was made along the course of the left sternomastoid down as far as the jugular notch. This was then curved downward over the left half of the sternum to the level of the second costal cartilage. This incision was carried into the deep planes of the neck anterior to the carotid sheath. The pretracheal muscles were separated from their origin from the sternum and the superior mediastinum was entered through the deep planes of the neck.

The esophagus was pulled out. There was actually about a 3 to 4 cm. length available to be used for the anastomosis. It was not possible to pull the stomach up through the apex of the thorax into the base of the neck and have room enough to perform an anastomosis. The attachments of the sternomastoid muscle and of the pectoral muscle to the inner third of the clavicle were separated from the bone and the pectoral attachment to the sternum was reflected laterally along with the fat and skin as a single flap. The medial third of the clavicle was resected and also the anterior half of the first rib. The prominent corner of the manubrium of the sternum which was left after disarticulating the first rib and the clavicle was cut wtih a bone cutter. This removal of portions of bone made a large round opening down to the pleura.

The pleura of the apex of the left pleural sac was then incised and the fundus of the stomach was grasped and pulled out through the wound. It was brought up into the neck without much difficulty and an esophagogastric anastomosis was performed on the posterior aspect of the fundus, using three layers of interrupted silk sutures. Instead of excising a circular portion of the gastric wall, a simple linear incision was used. By means of a series of sutures to adjacent fascial structures the fundus was supported in the base of the neck and following this the sternomastoid and pectoral muscles were sutured over in front of the stomach to the sternum and to the adjacent fascia. The fat and skin were then closed as separate layers using silk throughout. No drainage was used in the cervical wound.

The report of the pathologist after examination of the specimen revealed the tumor to be a squamous-cell carcinoma, grade 3, with metastasis to one regional lymph node.

The patient withstood the operation very well and made a good postoperative recovery. During the first four days of the postoperative course, particularly when he was turned on the left side, the pulse rate suddenly became very rapid at times and he had a marked fall in blood pressure. Both of these signs disappeared when he was turned on the back again. It was believed that this was due possibly to stimulation of the carotid sinus. The diet was advanced somewhat more slowly than in the average case of resection of the esophagus, but at the time of discharge from the hospital fourteen days after operation, the swallowing function was normal and he was taking a diet of finely chopped foods. Subsequent reports are that he has continued to improve. He eats normally and has gained weight and strength.

COMMENT

The operation described offers an acceptable method of treatment of carcinoma located in the superior mediastinal segment of the esophagus where resection with restoration of continuity of the alimentary canal has hitherto been impossible. It obviates the necessity of either a gastrostomy or a cervical esophageal stoma. The patient is enabled to swallow normally and to eat a normal diet. The functional result is good.

From the standpoint of long-time survival it is obvious that only the accumulation of experience with the use of this procedure in a group of patients

will prove its value. It should be pointed out, however, that unless the growth is early and small without evidence of local invasion of surrounding structures, the probability of local recurrence is great because of the fact that the dissection must of necessity be carried out close to the diseased area. This unavoidable fault is characteristic of all resections of the esophagus with the exception of those cases in which the growth lies near the cardia, but in the neck and superior mediastinum the narrowness of the operative field makes the difficulty even greater.

This fact, however, should not be allowed to militate against the decision to resect these tumors if it is at all possible to remove them. The pitiable plight of a patient with carcinoma of the esophagus who must die without the benefit of a resection should urge the surgeon on.

To cure such a patient is a blessing to be hoped for but probably not to be obtained in a large number of cases. To provide relief from dysphagia and to insure the comforts of normal eating are the greatest benefits which can be expected in the majority of cases. Those who are familiar with the end stages of this disease in the untreated patient will agree that this alone makes the operation worth while.

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STUDIES ON ONE HUNDRED FIFTY-ONE PATIENTS AT THE UNIVERSITY HOSPITAL IN RELATION TO THEIR DAILY WEIGHT FLUCTUATIONS

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THE following is a study made on all adult patients of the University Hospital at Minneapolis who had surgery performed on the stomach, colon, or rectum during the first six months of 1946. This group of patients was chosen because all of them were under the services of the same members of the surgical staff, and also because all of them were weighed daily during their stay in the hospital.

Each patient in this group was weighed, in so far as was possible, each morning after evacuation of the bladder and bowel and before they had been given their breakfast. All of those who were able to do so stood on the scale which was brought to the bedside, but for those patients who were unable to get out of bed a special scale was employed by means of which it was possible to weigh them in bed.

Concurrently with the record kept on their daily weight fluctuations, a record was kept of the total measurable fluid intakes and outputs of each patient both quantitatively and qualitatively.

During this same six-month period of time there was a total of 1,240 operations performed at the University Hospital on the Surgery service, and this group having surgery performed on the stomach, colon, or rectum numbered 151, or 12.17 per cent of the total.

All patients in this group were of the white race and their average age was 58.9 years. The sex distribution was as follows: ninety-seven, or 64.2 per cent, were males, and fifty-four, or 35.8 per cent were females. There were fourteen deaths, or a 9.4 per cent mortality in this series of patients.

The primary pathologic condition in these patients was as shown in Table I.

The type of operative procedure performed on these patients was as shown in Table II.

In the surgical procedures listed in Table II, it is to be noted that only the primary surgical procedure is included and such accompanying procedures (for example, the gastrojejunostomy performed at the time of a gastric resection) or additional procedures (for example, an incidental appendectomy) are omitted.

As mentioned previously, each patient is weighed in the morning before he is given any fluids either orally or parenterally; hence these weights are a measure of the physiologic activities of the day preceding.

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TABLE I

DIAGNOSIS	TOTAL	PER CENT
Gastric carcinoma	33	21.8
Duodenal ulcer	32	21.2
Rectal adenocarcinoma	22	14.6
Colonic carcinomas	19	12.6
Gastric ulcer	16	10.4
Ulcerative colitis	5	3.3
Gastric lymphosarcoma	4	2.6
Esophageal carcinoma	4	2.6
Rectal polyposis	3	2.0
Malfunctioning colostomy	3	2.0
Colonic polyposis	2	1.3
Tuberculous ulcer of colon	2	1.3
Rectovaginal fistula	1	0.7
Inflammatory colonic stricture	1	0.7
Ovarian carcinoma with spread	1	0.7
Chronic proctitis	1	0.7
Rectal lymphosarcoma	1	0.7
Colonic diverticula	1	0.7
Totals	151	100.0

TABLE II

OPERATION	NUMBER	PER CENT OF TOTAL
Subtotal gastrectomy	66	43.6
Partial colectomy	28	18.6
Colostomy or ileostomy	15	9.9
Abdominoperineal resection	8	5.4
Total gastrectomy	6	4.0
Total colectomy	5	3.3
Gastrojejunostomy	5	3.3
Gastrostomy	4	2.6
Colostomy closure	4	2.6
Exploratory laparotomy	3	2.0
Pull-through operation	2	1.3
Gastrotomy	2	1.3
Proctectomy	1	0.7
Proctotomy	1	0.7
Closure perforated duodenal ulcer	1	0.7
Totals	151	100.0

TABLE III

POSTOPERATIVE DAY OF WEIGHT LOSS	NUMBER	PER CENT OF TOTAL
1st	14	9.4
2nd	49	32.4
3rd	19	12.6
4th	13	8.6
5th	10	6.6
6th	2	1.3
7th	3	2.0
8th and after	6	4.0
Loss of less than 2½% total body weight	28	18.5
Not recorded properly	7	4.6
Totals	151	100.0

With this view in mind, it was noted that 116 of these patients, or 76.8 per cent, showed weight losses of as much as 2½ per cent of their total body weight following surgery. The day on which this loss occurred is listed in Table III.

The average amount lost by those patients who had a weight loss of as much as 2½ per cent of their total body weight was 2.3 kg. However, when computed on a percentage basis we have the findings shown in Table IV.

TABLE IV

PER CENT OF TOTAL BODY WEIGHT LOST	NUMBER	PER CENT OF TOTAL
Less than 2½	28	18.5
2½	37	24.6
3	18	11.9
3½	15	10.1
4	17	11.2
4½	6	3.9
5	16	10.6
6	6	3.9
Greater than 6	1	0.7
Not recorded properly	7	4.6
Totals	151	100.0

In an attempt to determine the cause of these losses in body weight the average intake for the day preceding the weight loss (see above) was determined and was found to be 3,292 c.c. The total output for this same day averaged 2,555 c.c. of which 70.5 per cent was urine, 27.6 per cent was from gastric suction, and 1.9 per cent was from other sources, such as emesis, bile, thoracenteses.

Since the greatest loss of fluid was from urine, it was thus considered necessary to determine those factors which might stimulate urinary output or which might cause retention of body water. To this end it was found that of the total fluid intake on the day preceding the weight loss, 51.3 per cent was 10 per cent glucose solution and this was given along with an average of 6.5 Gm. of sodium chloride. Thus, it seems that we here have an indictment against both the 10 per cent glucose and also against the small amount of sodium chloride given. In the case of the 10 per cent glucose, it cannot be stated that the blame must rest upon it per se because it must be taken into account that rapid administration of this solution is quite efficacious in causing diuresis.

In an attempt to determine what factors might be at play in those patients who did not have a weight loss, or whose weight loss exceeded 4 per cent, separate analyses were made of these two groups which comprised 18.5 and 30.3 per cent, respectively, of the total group of patients. For purposes of tabulation, the three groups are listed as follows in Tables V and VI.

A. Complete series of 151 patients.
B. Those patients whose weight loss was not as much as 2½ per cent or who showed an actual gain in weight.
C. Those patients whose weight loss exceeded 4 per cent of their total body weight.

TABLE V

	A	B	C
Average age	58.9 yr.	56.3 yr.	56.1 yr.
Sex: Males	64.2%	53.6%	68.1%
Females	35.8%	46.4%	31.9%
Average intake	3292 c.c.	3253 c.c	3478 c.c.
Per cent of intake which was 10% glucose	51.3%	51.3%	56.0%
Average output	2555 c.c.	1373 c.c	3025 c.c.
Per cent of output which was urine	70.5%	75.8%	69.3%

TABLE VI

OPERATION	A NO.	A PER CENT	B NO.	B PER CENT	C NO.	C PER CENT
Subtotal gastrectomy	66	43.6	13	46.5	21	44.7
Partial colectomy	28	18.6	6	21.3	12	27.7
Colostomy	15	9.9	2	7.1	1	2.1
Abdominoperineal resection	8	5.4	1	3.6	2	4.3
Total gastrectomy	6	4.0	3	10.8	4	8.6
Total colectomy	5	3.3	0	0.0	1	2.1
Gastrojejunostomy	5	3.3	1	3.6	1	2.1
Gastrostomy	4	2.6	0	0.0	1	2.1
Colostomy closure	4	2.6	0	0.0	1	2.1
Exploratory laparotomy	3	2.0	2	7.1	1	2.1
Pull-through operation	2	1.3	0	0.0	0	0.0
Gastrotomy	2	1.3	0	0.0	0	0.0
Proctectomy	1	0.7	0	0.0	1	2.1
Proctotomy	1	0.7	0	0.0	0	0.0
Closure perforated duodenal ulcer	1	0.7	0	0.0	0	0.0
Totals	151	100.0	28	100.0	46	100.0

Statistically analyzed none of the minor variations noted here among the three groups is significant, with all three showing the same general trends and tendencies, except for the fact that in those patients who did not lose as much as 2½ per cent of their total body weight there was a marked diminution in total fluid output, and in those patients showing a weight loss of as much as or more than 4 per cent there was a slight increase in the average fluid output.

CONCLUSIONS

A study was made on all adult patients having surgery performed on the stomach, colon, or rectum during the first six months of 1946 in relation to their daily weight fluctuations. This group of patients comprised 12.17 per cent of all patients undergoing surgery in the main operating rooms at the University Hospitals during the same period of time. (Orthopedic, gynecologic, and otorhinolaryngologic surgery are performed in their own operating rooms.) There were fourteen deaths, or a 9.4 per cent mortality in this series of patients.

One hundred sixteen, or 76.8 per cent, of these patients showed a weight loss of as much as 2½ per cent of their body weight in the immediate postoperative period. Eleven, or 7.3 per cent of these patients, showed weight gains of 2.5 per cent or more of their body weight, and seventeen, or 11.2 per cent of the patients, showed no weight loss or gain of as much as 2½ per cent of their body weight, or their weight fluctuations bore no relation to any operative procedure.

The day on which the largest percentage of patients lost weight was the second postoperative day. Since the weights are taken each morning, however, this indicates that the greatest loss occurs on the first day following surgery.

The average weight loss per patient was 2.3 kg. The average fluid output on the day of weight loss was 2,555 c.c., of which 70.5 per cent was urine.

The average fluid intake on the day of weight loss was 3,292 c.c., of which 51.3 per cent was 10 per cent glucose, 27.7 per cent was 5 per cent glucose, 12.2 per cent was normal saline solution, 5.2 per cent was water (per os), 1.8 per cent was 5 per cent amigen, and the rest was hospital diet II.*

Separate analyses of those groups of patients who showed no significant weight loss and of those whose weight loss exceeded 4 per cent of their total body weight revealed no significant factors in these groups which might make them differ from the original group, except for the fact that the average output on those patients who had no significant loss in weight was approximately one-half that of the average output of the whole group, and that the average output on those patients showing a weight loss greater than 4 per cent of their total body weight was approximately 25 per cent greater than that of the average output of the whole group.

*Varco, R. L.: Preoperative Dietary Management for Surgical Patients, SURGERY **19**: 303, 1946.

PRODUCTION OF GASTRODUODENAL ULCERS IN THE DOG BY CONTINUOUS SUBCUTANEOUS OR INTRAVENOUS ADMINISTRATION OF HISTAMINE

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CONTINUED excessive secretion of highly acid gastric juice is considered to be an important factor in the pathogenesis of peptic ulcer Since histamine strongly stimulates the secretion of HCl by the parietal cell, investigators have used this substance in attempts to produce ulceration of the gastrointestinal tract experimentally in animals. There are reports of erosions or ulcers found in guinea pigs, cats, and dogs after injections one or more times daily for varying periods of time, but workers in this laboratory were unable to obtain ulcers in dogs, although erosions were observed, even when 2 mg. of histamine dihydrochloride were injected every two hours, ten times a day, for over two months.[1]

Intramuscular injections of a histamine and beeswax mixture as prepared by Code and Varco,[2] in amounts of 30 to 40 mg. of histamine base daily, have been shown regularly to produce ulcers in dogs[3] and, with appropriate doses, in a variety of other animals.[4] The histamine-beeswax preparation provides for a slow release of the drug and a sustained stimulation of gastric secretion throughout the twenty-four hour period.[2] It appears from these results that a continuous histamine action is necessary for the production of experimental ulcer in the dog and that periodic subcutaneous injections of aqueous histamine solutions, even at two-hour intervals, do not satisfactorily produce such an action.

In the experiments to be described we have injected histamine *continuously* into a group of dogs by the subcutaneous route to determine whether ulcers would occur when the drug was so administered. Into another group of dogs we have injected histamine *continuously* intravenously to test, by comparison of results obtained with the two methods, the possibility that an ulcerogenic agent is released from the tissues in the course of the local reaction to histamine or beeswax. Although Varco and associates[4] have shown that beeswax injection alone will not cause ulceration, it is conceivable that two factors—histamine and some ulcerogenic agent released from the tissues—together might be responsible for the histamine ulcer.

We hoped from these experiments to find what dose-time relationships exist with respect to ulcer production in the dog and especially what minimal amount of histamine will cause ulceration within a limited period of time.

Procedure.—Dogs weighing from 5 to 14 kilograms were given the continuous subcutaneous injections of histamine through a 3 inch long, 21 gauge needle inserted into the back and secured with straps. The position of the needle was changed every twelve hours, and the injection sites were shaved and washed with iodine and alcohol before inserting the needle.

Dogs which were to receive intravenous injection were anesthetized with sodium pentobarbital and an area at the base of the neck overlying an external jugular vein was prepared for surgery. The vein was exteriorized through a longitudinal incision and was clamped. A flexible plastic tubing ($\frac{3}{64}$ inch inside

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diameter with walls 1/64 inch thick) was inserted for a distance of 4 or 5 inches through a small hole made in the vein proximal to the clamp. The clamp was then removed and after replacing the vein, the incision was sutured, a length of tubing extending out through the skin. In some cases the vein was tied off distal to the point of tube insertion and sutures were also tied around the vein containing the plastic. A protective tight-fitting rubber tubing, previously adjusted, covered the length of plastic tubing which extended out from the vein. To secure the assembly, sutures were passed through the skin and tied to a wire loop at the end of this rubber tubing which touched the skin and the tubing was then fixed to the neck or shoulder with collodion-soaked gauze.

The subcutaneous needle, or the needle inserted into the open end of the plastic tubing, was connected by rubber tubing to a graduated container suspended about six feet above the animal. Solution delivery was accomplished by gravity and the rate was controlled by a screw clamp and calibrated drop counting apparatus. In some experiments instead of gravity drip, we employed very satisfactorily a fluid pump described by Bratton.[5] Saline solution alone was given to "intravenous" dogs for one day following preparation to permit recovery from the sodium pentobarbital.

Sterile solutions of histamine dihydrochloride* in 0.9 per cent NaCl were injected at rates of from 240 to 960 c.c. per twenty-four hours, the smaller volumes being given by the subcutaneous method.

All but the first few dogs were given a vermifuge several days before starting the experiment to remove the complicating factor of intestinal worms which may cause or predispose to ulceration.

Drug administration was continuous, in so far as was possible, from the beginning of the experiment until death or until the animals were sacrificed, usually after twenty-one days.

RESULTS

Subcutaneous Injection.—Histamine dihydrochloride was injected continuously into eighteen dogs, the daily doses ranging from 36 to 7 mg. of histamine base.† Five animals were sacrificed after fourteen to twenty-one days; the remainder of the animals died during the course of the experiment. At autopsy after injection periods of from forty-one hours to twenty-one days, ulcers were found in twelve of these dogs, ulcer perforation occurring in seven animals. Erosions or duodenitis, or both, were observed in the dogs with ulcers and in five of the six animals which did not develop ulcers. Varying degrees of colitis appeared in some of the animals. One dog exhibited no apparent lesions.

Ulcerations were frequently multiple and varied in size from acute lesions less than 0.5 cm. in diameter to deep craters 1.5 to 2 cm. across, the greater dimension usually being along the longitudinal axis. The larger ulcers had flat hard bases and raised indurated edges; the craters were sometimes filled with debris or blood clots. Ulcers regularly developed on the posterior wall of the duodenum within 0.5 to 3 cm. of the pyloric sphincter, and often a "kissing" ulcer was found on the opposing portion of the anterior wall. In one case a

*Imido "Roche," the histamine used in these studies was supplied by the Hoffmann-LaRoche, Inc., Nutley, N. J.

†All dose values are in terms of histamine base.

single ulcer occurred on the anterior wall of the duodenum. Ulcers were found at the pyloric sphincter in two dogs and in the pars intermedia of one dog. Two dogs had esophageal ulcers, one of which had perforated.

The weights of twelve animals were taken at the beginning of the experiment and again at death, from which data the average weight of the animal was determined by assuming a uniform weight change throughout the experiment. Using these average weights it was possible to estimate the rate of histamine administration for these twelve dogs in terms of micrograms histamine base per kilogram body weight per minute. Reference to Table I shows that in this series of dogs, ulcers developed within two weeks or less with doses of over 1 microgram histamine per kilogram per minute while they usually did not occur when lesser amounts were given. However, two dogs, No. 4 and No. 12, receiving the larger doses died after 4 and 6.5 days of injection without ulcers, and two dogs, No. 17 and No. 18, given the smaller doses of histamine did develop ulcers. There was then no strict correlation between the histamine dose and ulcer development, but in general the number and severity of ulcerations and the rapidity of their onset (as indicated by autopsy at death) were greater, the larger the histamine dose.

TABLE I. EFFECT OF CONTINUOUS SUBCUTANEOUS HISTAMINE

DOG NO.	AVERAGE BODY WEIGHT	HISTAMINE DOSE*		DAYS	CONCLUDED BY	RESULTS
		MG. PER DAY	MICROGRAMS KG. PER MIN.			
1		36		1.5	Death	Perforated ulcer at pyloric sphincter
2		30.5		2.5	Death	Multiple ulcers of duodenum; perforated esophageal ulcer†
3		30		6.0	Death	4 duodenal ulcers, 1 perforated
4		27		4	Death	Duodenitis only
5		24		13.5	Death	5 duodenal ulcers, 1 perforated; 1 acute ulcer pars intermedia
6		23		4.0	Death	2 duodenal ulcers, 1 perforated esophageal ulcer
7	6.6	22	2.3	2.0	Death	2 duodenal ulcers
8	5.4	19.5	2.5	7.5	Death	Multiple duodenal ulcers, 1 perforated
9	8.6	18.5	1.5	12.5	Death	3 acute duodenal ulcers
10	6.6	16.5	1.7	10.5	Death	2 duodenal ulcers, 2 ulcers at pyloric sphincter
11	9.0	16	1.2	15.5	Death	8 duodenal ulcers, 1 perforated†
12	7.0	13.5	1.3	6.5	Death	No cause of death found
13	11.2	11.5	0.71	21.0	Sacrifice	3 duodenal erosions
14	6.3	8.5	0.94	9.5	Death	1 duodenal erosion
15	6.4	8	0.86	20.5	Sacrifice	Duodenitis only
16	6.6	8	0.82	20.5	Sacrifice	Duodenitis only†
17	7.6	7.5	0.70	14.0	Sacrifice	1 duodenal ulcer
18	7.8	7.0	0.64	21.0	Sacrifice	2 duodenal ulcers

*In terms of histamine base.
†Worms were found in the intestines of these dogs.

Vomiting occurred in the dogs found at autopsy to have ulcers, but seldom occurred in animals which did not develop ulcers, and anorexia usually accompanied or soon followed the initiation of vomiting; duodenitis and colitis frequently occurred. Pulmonary edema or pneumonia and emphysema developed in the lungs of eight of thirteen animals examined for the condition, and these complications were probably responsible for the death of some of the dogs.

Subcutaneous inflammation was found at injection sites in the majority of the animals and was not prevented in four dogs when 100 units of penicillin per cubic centimeter was added to the solution being injected.

Intravenous Injection.—Histamine was administered intravenously and continuously in sixteen dogs, in doses of from 36 to 7.5 mg. of base per day. Seven animals were sacrificed; the remainder died during the course of the experiment. Thirteen animals developed ulcers within sixteen days or less and perforations occurred in three dogs. Of the three dogs without ulcers, one had gastric and duodenal erosions, another duodenitis, and the third exhibited no lesions.

The distribution and the type of ulcers resulting from intravenous histamine injection were similar to that following subcutaneous histamine. The ulcers usually developed on the posterior wall of the duodenum within 1 to 3 cm. below the pyloric sphincter, and a "kissing" ulcer was found on the anterior wall in four dogs. In three dogs ulcers appeared at the pyloric sphincter. Ulceration occurred in the stomachs of two dogs. One had a small lesion 0.5 cm. above the pyloric sphincter while the other had four ulcers at a distance of 6 cm. above the pyloric sphincter, two of which ulcers had perforated. This latter finding is of interest and significance. The position of these four ulcers corresponded exactly to the openings in a Rehfuss tube olive, which had been put in the dog's stomach for aspiration of gastric juice during an acute experiment performed the day before beginning continuous histamine injection. These ulcerations clearly indicate that the factor of mucosal injury can play a role in the production of experimental ulcers.

A conclusion as to a minimal adequate dose of intravenous histamine is not warranted as can be seen by reference to Table II. The data suggest that doses

TABLE II. EFFECT OF CONTINUOUS INTRAVENOUS HISTAMINE

DOG NO.	AVERAGE BODY WEIGHT	HISTAMINE DOSE*		DAYS	CONCLUDED BY	RESULTS
		MG. PER DAY	MICROGRAMS KG. PER MIN.			
1		36		3.5	Sacrifice	2 ulcers of duodenum
2	7.6	35.5	3.3	12	Sacrifice	3 ulcers of duodenum, 1 perforated
3	7.4	34	3.2	5	Death	1 acute ulcer of duodenum, 1 acute ulcer of stomach, pyloric
4	5.2	31.5	4.2	4	Death	1 ulcer of duodenum, 2 acute ulcers of pyloric sphincter
5		27.5		4.5	Death	3 ulcers of duodenum,† 1 ulcer of pyloric sphincter
6	11.8	27	1.6	13.5	Sacrifice	2 acute ulcers of duodenum
7	8.9	26	2.0	19.0	Sacrifice	No lesions
8	7.1	18	1.7	3	Death	1 ulcer of duodenum
9	12.3	18	1.0	6	Death	1 perforated ulcer of duodenum
10		16		16	Sacrifice	1 ulcer of duodenum
11	8.1	13	1.1	4	Death	1 ulcer of duodenum
12	5.4	10.5	1.4	2	Death	4 ulcers of stomach, 2 perforated
13	14.1	8.5	0.43	9	Sacrifice	Duodenitis only
14	10.4	8	0.52	11	Death	3 acute ulcers of duodenum
15	6.9	7.5	0.74	9	Death	1 acute ulcer of pyloric sphincter
16	7.7	7.5	0.67	21.5	Sacrifice	Erosions of stomach and duodenum

*Doses are in terms of histamine base.
†Worms were found in the intestine of this dog.

of less than 1 microgram histamine per kilogram per minute were less effective in causing ulcers, but there was imperfect correlation between the size of dose and the onset or severity of ulceration. Reasons for this apparent lack of correlation will be discussed later.

The lungs of most of the dogs receiving histamine intravenously showed congestion, emphysema, and infarcts, the latter probably caused by emboli originating from thrombi caused by the plastic tubing in the jugular vein. Usually there was some inflammation of the skin, subcutaneous tissues, and vein at the site of tube insertion.

Vomiting or evidence of vomiting was noted in eight of the thirteen dogs developing ulcer, but was not observed in those animals which did not develop ulcers. Anorexia usually accompanied or shortly followed the vomiting.

Gastric Secretory Response.—In several animals the rate of gastric secretion in response to the continuous administration of histamine was determined at

TABLE III. GASTRIC RESPONSE TO CONTINUOUS INTRAVENOUS OR SUBCUTANEOUS HISTAMINE

EXPERIMENT AND DOG NO.	DAY OF EXPERIMENT	SAMPLE	VOL. (C.C. PER HR.)	TOTAL ACID (MEQ. HCL PER LITER)	REMARKS
I. V. No. 10	7	Resid. 17 c.c.		130	Sacrifice 16 days; ulcer; duodenum
		10 min.	30	124	
		20 min.	72	132	
		30 min.	75	136	
	12	Resid. 5.5 c.c.		129	
		10 min.	33	98	
		20 min.	27	122	
		30 min.	30	117	
I. V. No. 9	4	Resid. 11 c.c.		37	Death 6 days, perforated ulcer of duodenum
		10 min.	39	33	
		15 min.	84	14	
		20 min.	54	24	
I. V. No. 16	20				Sacrifice 21 days, erosions, stomach and duodenum
		10 min.	51	83	
		20 min.	60	116	
		30 min.	66	109	
S. C. No. 15	10	Resid. 9 c.c.		95	Sacrifice 20.5 days, duodenitis only
		15 min.	28	107	
		25 min.	45	114	
	13	Resid. 6.3 c.c.		113	
		10 min.	34	120	
		25 min.	28	129	
		35 min.	42	123	
S. C. No. 16	10	Resid. 9.5 c.c.		73	Regurgitation, stopped analysis
	13	Resid. 5.0 c.c.		80	
		10 min.	11	72	
		Relavage	17	73	All but 1st sample stained with bile, last sample blood stained; sacrifice 20.5 days, duodenitis only
		15 min.			
		25 min.	10	90	
		35 min.	12	35	
I. V. No. 5	2	Resid. 3.2 c.c.		92	Death 4.5 days; ulcer, duodenum
		10 min.	13	118	
		12 min.	30	114	
		20 min.	43	148	
		25 min.	49	146	
I. V. No. 1	2	10 min.	54	122	Sacrifice 3.5 days; ulcers, duodenum
		20 min.	33	132	
		30 min.	8	128	
		40 min.	45	97	
		50 min.	36	137	All samples bile stained

varying intervals after the beginning of the experiment. This was accomplished by introducing a Rehfuss tube into the stomach with the dog in a fasting state. The results of these tests are shown in Table III. It is of interest to compare these results with the values we[15] have obtained in similar experiments upon intact dogs receiving histamine for only short periods. In these short-term studies it was found that the response to a supramaximal dose of histamine varied from 38 to 102 c.c. with an average of 76 c.c. per hour and a total acidity of from 114 to 148 meq. with an average of 137 meq. per liter. In the present studies the values for the concentration of acid fall mostly within this range whereas the volumes are, on the average, distinctly lower than those found in the normal dog.

DISCUSSION

Some factors should be mentioned which partially obscure the dose-time relationship with respect to ulcer production and prevent the establishment of an exact minimal histamine dose which will cause ulceration within the period of time set in these experiments. In some cases histamine delivery was temporarily stopped by movements of the dogs which twisted the tubing. The importance of continuous administration of histamine is emphasized by the fact that in the experiments of Orndorff and co-workers[1] ulcers were not produced by 12 mg. of histamine base per day given in ten doses at two-hour intervals, whereas we have obtained ulcers with total daily doses equal to or smaller than this by continuous subcutaneous or intravenous administration. However, ulcer incidence at this dose level was low and we suspect that Orndorff and associates were not giving large enough doses of histamine. It is possible that they would have obtained some ulcers even with intermittent administration, had they given more of the drug.

Pulmonary complications, which often developed, may have enhanced the effect of histamine to cause ulceration, and furthermore the results suggest to us that some variation occurred in the susceptibility of different healthy dogs to the ulcer-producing effects of histamine.

Discrepancies in the correlation between histamine dose and ulcer production, due in part to the factors mentioned, make impossible any close comparison of the results obtained by subcutaneous and intravenous histamine injection. It is our opinion that the ulcers following intravenous histamine administration were smaller and less severe, an opinion borne out to some extent by the finding that ulcer perforation occurred in only three animals as compared to perforation in seven dogs given subcutaneous histamine. But discontinuity of drug administration occurred more often in dogs given histamine intravenously. On the basis of these experiments, we do not believe the evidence indicates that an ulcerogenic agent is released from the tissues to increase the ulcer-producing effects of histamine. On the other hand, in producing ulcers by intravenous histamine injection, the possibility that a secondary ulcerogenic agent is acting has not been completely eliminated because some inflammation did occur around the plastic tube in the jugular vein.

We may now ask, "Why does histamine administration cause an ulcer?" A general statement of the possibilities may help answer this question. Ulceration of the gastrointestinal tract is the end result of destruction and loss of

mucosal tissue more rapidly than it is replaced by reparative mucosal proliferation. Normally ulcers do not occur because the combination of cellular resistance and reparative mechanisms effectively counterbalances destructive or potentially destructive processes. Histamine must then upset this balance by increasing the destructive agency or decreasing the specific resistance of mucosal cells, or it may act to slow up the proliferative processes. Finally, the action may be a combination of more than one, even all, of these possibilities.

The necrosing and erosive properties of an acid-pepsin gastric juice are unquestioned. Histamine causes the secretion of large volumes of highly acid gastric juice as well as an increase in the secretion of pepsin[6] although the concentration of this enzyme in histamine-stimulated gastric juice is low due to a relatively greater increase in parietal cell secretion. A limited number of experiments by Shoch and Fogelson suggests that histamine ulcer may be delayed by the oral administration of a pepsin-inactivating substance,[7] but as has been stated by one of us,[8] although pepsin increases the destructive properties of acid gastric juice the evidence indicates that HCl alone is sufficient to cause damage to the intestinal mucosa under proper conditions. We have found by aspiration of gastric juice a continued good secretory response with respect to acid values after two weeks of histamine administration. In spite of this continued insult to the intestinal mucosa, ulcers did not always occur. This suggests that some other factor may be necessary for the development of ulceration. The possibility exists that histamine, in addition to increasing the amount of gastric juice which the mucous membrane must withstand, also decreases the resistance of the mucosa by interfering with protective mechanisms such as alkaline secretions or blood supply or with the reparative process.

Merkel[9] and other German workers, Heinlein and Kastrup,[10] have described histologic and physiologic changes in the gastric and duodenal mucosa of guinea pigs, dogs, and cats following histamine injection. The changes reported are hyperemia, edema, thrombosis, and necrosis of the mucosa and submucosal tissues with ultimate sloughing of the mucosa. These pathologic changes have been ascribed to an angiotoxic action of histamine and may be due to the vasodilatation and increased permeability of the capillaries with a resulting decrease in the nutritive supply to the cells of the mucosa.

Loew,[11] in a comprehensive review of antihistamine drugs, cited reports of a number of workers that these substances decrease or inhibit the vasodilation and increased permeability of capillaries following histamine administration. Benadryl does not, however, prevent histamine ulcers in guinea pigs[12] or dogs.[13]

Kahlson[14] has reported an adaptation of capillaries to continued histamine administration but it is possible that adequate readjustment may not occur.

Two lines of evidence bear upon the hypothesis that some factor in addition to hypersecretion operates in the production of ulcers by histamine. First, we have found in experiments on intact dogs[15] that the maximal gastric secretory response to subcutaneously injected histamine is obtained with a dose of about 1 microgram per kilogram per minute. Yet reference to Table I clearly reveals that continuous doses of histamine larger than this value increase the severity and rapidity of onset of ulceration. Second, Cummins[16] has found that ulcers are rapidly produced when 0.1 N HCl is infused into a dog's stomach by

way of a fistula, but that when the acidosis accompanying this addition of HCl is prevented by injecting equivalent amounts of base intravenously, the ulcers do not develop. This indicates the effect which metabolic disturbances may have upon the resistance of the mucosa to digestion. Hale[17] has shown on four dogs that continuous administration of histamine does not produce acidosis. On the contrary a moderate degree of alkalosis occurred, and two of these dogs developed ulcers.

We suggest that histamine may exert a toxic effect disposing to ulceration by some disturbance of the body tissue metabolism which decreases cellular resistance to digestion and perhaps also decreases the normal repair processes, thereby increasing the vulnerability of the intestinal mucosa to the action of gastric juice.

SUMMARY AND CONCLUSIONS

1. Ulcers have been produced regularly in the duodenum and occasionally in the stomach of the dog by the continuous subcutaneous or intravenous administration of aqueous histamine solutions in doses of one or more micrograms of histamine base per kilogram per minute for periods ranging from two to sixteen days. Effective doses of subcutaneously administered histamine are in the range of those found to produce a maximal gastric secretory response in the dog.

2. Increasing the rate of continuous histamine administration above that which produces maximal gastric secretion increases the severity and rapidity of onset of ulceration, indicating that histamine exerts some additional action to decrease the resistance of the intestinal mucosa to the destructive effect of the gastric juice.

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STUDIES IN NITROGEN METABOLISM

Influence of Caloric Intake and the Route of Administration of Amino Acids Upon Nitrogen Balance: The Effect of Nitrogen Intake Upon Food Intake

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DURING several years of experimental work in problems related to nitrogen balance, there was frequent occasion to question certain concepts which have been generally accepted. (1) The importance of carbohydrate intake in protein metabolism[1-7] has long been established. The relationship has influenced programs of amino acid administration, but we are not aware of any detailed study of the relationship of the caloric intake to nitrogen balance at different levels of carbohydrate consumption, the protein and fat in the diet remaining unchanged. (2) Elman and associates[8] and Shohl[9] indicated that a given protein digest produces the same nitrogen retention, regardless of whether it is administered intravenously or orally. This finding is in marked variance with the experience of Madden and his co-workers[10] and with our own.[11] (3) Many clinicians are of the opinion that the intravenous administration of casein digests may incur a decreased food intake.[12, 23]

Hence, in the course of other nitrogen balance experiments, we planned a study designed to evaluate each of these three concepts.

METHODS

Three groups of experiments were carried out on twenty-five patients presenting various degrees of protein deficiency. Although these patients may appear to be of a heterogeneous group, they actually were not since all were protein-deficient. They were selected for these studies for two reasons: first, the results obtained would apply directly to the type of patient for whom amino acid therapy is customarily indicated; second, in another investigation in which the biologic value of the same amino acid preparation used in this study was determined,[13] a remarkable constancy of results was observed between different types of protein-deficient patients.

A diet was selected which consisted chiefly of carbohydrate. Fat was allowed in quantities of 20 to 40 Gm. per day, and the extraneous oral nitrogen intake was limited to less than 500 mg. per day; the latter consisted for the most part of the incomplete protein of vegetables and fruits. When the protein digest*

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*Amino Acids, I.C., lyophilized (for intravenous use), provided by Interchemical Corporation, Union, N. J.

was administered intravenously, as in the first experiment, it was given at a level of between 129 and 166 mg. of nitrogen daily per kilogram of body weight; this level had been determined from figures obtained in previous studies, in which the minimal quantity of the preparation required for nitrogen equilibrium was determined. The digest was administered in 5, 7.5, or 10 per cent solution in distilled water, at a rate of 20 to 25 Gm. per hour, for periods of between three and five days, for each level of intake. In the study comparing oral and intravenous routes of administration, the same material (originally manufactured for intravenous use) was given orally in identical amounts (dissolved in distilled water) as three divided doses at each mealtime; it was followed by a carbohydrate beverage as a "chaser." During the period of study, all patients were given parenterally 500 mg. of ascorbic acid and 1 c.c. of "Bejectal"* daily.

The study was performed with the use of a metabolic unit staffed by special nurses and a dietician. Representative diets were submitted for nitrogen analysis, as were all urines and stools collected during each twenty-four hour period. Methods of analysis were the same as described in previous studies.[11, 13]

RESULTS

Influence of Caloric Intake Upon Nitrogen Balance.—This phase of the study was carried out on five patients, at levels of caloric intake indicated in Table I. Each period of study lasted five days.

In three of the five patients, the caloric intake (exclusive of protein) was started at 1,500 calories per day, and increased 500 calories at a time for three succeeding periods until the level of 3,000 calories was reached. This level

TABLE I. EFFECT OF CALORIC INTAKE ON NITROGEN BALANCE

		CALORIC INTAKE CALORIES PER DAY				NITROGEN			
						INTAKE		EXCRETION	BALANCE
PATIENT	NO. OF DAYS	DIET	INTRAVENOUS AMINO* ACIDS	TOTAL	CALORIES PER KG. BODY WT.	MG. PER KG. PER DAY	GM. PER DAY	GM. PER DAY	GM. PER DAY
J. E.	5	1503	240	1743	37	162	7.6	9.1	−1.5
	5	2028	240	2268	48	166	7.8	8.8	−1.0
	5	2569	240	2809	60	166	7.8	8.3	−0.5
	5	3024	240	3264	70	166	7.8	8.2	−0.4
F. S.	5	1508	224	1732	30	129	7.3	6.1	+1.2
	5	1997	224	2221	39	129	7.3	7.0	+0.3
	5	2508	224	2732	48	129	7.3	6.4	+0.9
	5	2992	224	3216	57	130	7.4	6.6	+0.8
F. R.	5	1508	248	1756	32	145	8.0	9.0	−1.0
	5	1997	248	2245	41	145	8.0	8.7	−0.7
	5	2508	248	2756	50	143	7.9	9.4	−1.5
	5	3022	248	3270	60	142	7.8	8.4	−0.6
T. K.	5	3013	236	3249	58	143	8.0	7.1	+0.9
	5	995	236	1231	22	143	8.0	9.0	−1.0
M. J.	5	3007	188	3195	79	158	6.4	5.8	+0.6
	5	2025	188	2213	55	158	6.4	5.8	+0.6
	5	1004	188	1192	25	158	6.4	5.6	+0.8
	5	501	188	689	12	158	6.4	6.4	0

*Provided by Interchemical Corporation; amino acids, I.C., lyophilized.

*Furnished by Winthrop Chemical Co., Inc., New York, N. Y.; 1 c.c. furnishes 5 mg. thiamin, 5 mg. riboflavin, 5 mg. pyridoxine, 5 mg. calcium pantothenate, and 50 mg. Niacin.

was found to be the ceiling of tolerance for most patients on a diet consisting chiefly of carbohydrate beverage. Patient J. E. appeared to have a slightly less negative nitrogen balance as the calories increased but the reverse situation was found in the next two patients, F. S. and F. R. Two (J. E. and F. R.) never attained positive nitrogen balance.

If the caloric value of protein is considered, each of the three patients mentioned received 30 calories per kilogram per day as the minimal caloric intake, which fact might explain the negative results obtained. Accordingly, the reverse experiment was planned in which a 3,000 caloric diet was progressively decreased to the lowest level tolerated. One patient (T. K.) refused to cooperate after five days of the 3,000 calorie regimen and accepted an average of only 995 calories for the next five days; his average daily positive nitrogen balance of 0.9 Gm. per day dropped to a negative balance of 1.0 Gm. per day. In the remaining patient (J. J.) there was no significant difference between the degree of nitrogen balance on 3,000 and 1,000 calorie regimens, but when the calories were decreased to approximately 500 per day exclusive of protein (or 12 calories per kilogram including protein), positive balance was no longer tenable.

Influence of Oral and Intravenous Routes of Amino Acid Administration Upon Nitrogen Balance.—Eight patients were studied, four of whom had been in the previous program. Periods of study were the same, or approximate, for each route of administration, as shown in Table II. For all patients, that level

TABLE II. COMPARISON OF INTRAVENOUS AND ORAL ADMINISTRATION OF AMINO ACIDS*

				NITROGEN			
				INTAKE		EXCRETION	BALANCE
PATIENT	ROUTE OF ADMINISTRATION	NO. OF DAYS	TOTAL CALORIC INTAKE	MG. PER KG. PER DAY	GM. PER DAY	GM. PER DAY	GM. PER DAY
T. S.	I. V.	5	3216	130	7.4	6.6	+0.2
	Oral	5	3238	139	7.9	5.7	+2.2
F. R.	I. V.	5	3270	142	7.8	8.4	−0.6
	Oral	5	3246	142	7.8	6.7	+1.1
T. K.	I. V.	5	1231	143	8.0	9.0	−1.0
	Oral	5	1251	143	8.0	6.0	+2.0
M. J.	I. V.	5	3195	158	6.4	5.8	+0.6
	Oral	5	3130	156	6.3	3.9	+2.4
J. W.	I. V.	3	3356	123	5.3	5.7	−0.4
	Oral	3	3385	123	5.3	4.3	+1.0
	I. V.	3	2439	153	6.6	6.0	+0.6
	Oral	3	2440	153	6.6	4.0	+2.6
J. T.	I. V.	3	2294	117	6.5	5.5	+1.0
	Oral	5	2189	117	6.5	5.1	+1.4
	I. V.	3	2479	292	16.2	15.2	+1.0
	Oral	5	2472	290	16.1	9.9	+6.2
M. T.	I. V.	3	2248	160	8.0	5.9	+2.1
	Oral	4	2248	162	8.1	5.5	+2.6
	I. V.	3	2446	290	14.6	12.2	+2.4
	Oral	5	2443	290	14.6	8.6	+6.0
V. E.	I. V.	3	2241	203	8.0	4.9	+3.2
	Oral	4	2248	206	8.1	6.7	+1.4

*Provided by Interchemical Corporation and prepared for intravenous use.

of amino acids was selected which was believed on calculation to be sufficient to maintain equilibrium. Caloric intake was leveled to the patient's desire, but was kept constant for each period of study. In three patients, the same study was repeated at a higher level of amino acid intake.

In three of the eight patients, oral administration produced positive nitrogen balance at the level of amino acids given, whereas the same level given intravenously did not. In seven of the eight patients, the degree of positive balance was greater with the oral route than with the intravenous; this difference was even more marked at the higher level of nitrogen intake (Table II) (J. W., J. T., M. T.). In the one patient in whom the intravenous route produced a higher level of positive nitrogen balance, both routes produced positive balance.

Influence of Nitrogen Intake Upon Caloric Intake.—These data were obtained in the course of another study[13] in which the "nitrogen balance index"

TABLE III. CALORIC INTAKE (EXCLUSIVE OF PROTEIN) IN TWENTY PATIENTS AT VARIOUS LEVELS OF INTRAVENOUS AMINO ACIDS ADMINISTRATION

CASE		DAILY DOSE OF AMINO ACIDS (GM.)						CHANGE IN WT. AT END OF STUDY (KG.)
		0	25-35	50-70	80-100	100-120	120+	
1	Av. No. of calories per day	2099	2661	1676	1529	----	----	-1.8
2	Av. No. of calories per day	2073	1571	1716	1938	1778	1908	-2.0
3	Av. No. of calories per day	3458	2010	2500	2384	----	1347	-2.0
4	Av. No. of calories per day	1316	1247	1695	1251	----	1370	+3.1
5	Av. No. of calories per day	2213	1950	2342	2503	2684	----	+2.0
6	Av. No. of calories per day	3119	2327	3933	3538	----	3460	+2.6
7	Av. No. of calories per day	680	800	850	1177	----	----	-1.9
8	Av. No. of calories per day	2038	1838	2026	2172	1819	2147	-0.5
9	Av. No. of calories per day	1825	1913	1784	1424	----	----	+1.7 (Ascites?)
10	Av. No. of calories per day	1696	2182	2565	2812	2298	----	+0.8
11	Av. No. of calories per day	2010	2183	2265	2294	2219	----	-2.1
12	Av. No. of calories per day	2024	1923	2265	2384	----	----	+0.8
13	Av. No. of calories per day	2011	2148	2310	2110	1944	----	+1.0
14	Av. No. of calories per day	2038	2052	2055	1985	1974	----	-3.2
15	Av. No. of calories per day	2018	2222	2239	----	1610	----	+0.9
16	Av. No. of calories per day	2011	2023	2005	----	2007	1231	+1.0
17	Av. No. of calories per day	2006	2015	2000	----	2006	----	+1.9
18	Av. No. of calories per day	2003	1992	2000	----	2006	----	-0.8
19	Av. No. of calories per day	1953	2088	1559	----	1187	1069	+1.2
20	Av. No. of calories per day	1818	2004	2033	----	----	----	+1.8

of the amino acid preparation under investigation was determined in the human protein-deficient patient. This experiment requires the administration of the protein at carefully graded levels, starting at those known to create a negative balance. An opportunity was afforded to observe the effect of increasing the protein intake upon the voluntary ingestion of other calories, chiefly in the form of a carbohydrate beverage. Twenty such patients were available for study, as presented in Table III.

Seven of the twenty patients showed a decreased voluntary caloric intake at one or more levels of amino acid intake. In three of these, there resulted a loss in weight of 1.8 to 2.0 kilograms. In eight patients, the caloric intake did not fluctuate more than 200 calories per day. In the remaining five, there was an actual increase of calories consumed. Although the decrease in caloric intake usually occurred at the peak of amino acid intake, the rise in caloric intake not infrequently occurred at this point as well. In a separate study on this group of patients, no correlation was seen between the caloric intake and the degree of positive nitrogen balance or protein regeneration.[13]

DISCUSSION

The effect of carbohydrate intake upon protein nutrition was first noted by Rubner as early as 1883.[2] He found that the protein metabolism of the fasting dog could be reduced when carbohydrate was fed. Lusk[1] in 1890 demonstrated, in an experiment on himself, that with sudden withdrawal of carbohydrate from the diet, the protein metabolism was definitely increased. Zeller[14] noted that not until carbohydrate intake was reduced to less than 10 per cent of the total caloric intake was protein metabolism affected. Rubner[15] was able to decrease caloric requirements by 33 per cent without influencing nitrogen balance. Block[16] found that so long as he maintained the protein intake of six patients at 1 Gm. or more per kilogram per day, he could reduce the caloric intake from 80 per cent to 20 per cent of basal needs and in the majority of instances still attain positive nitrogen balance. Elman[17] found that if the amino acid intake of dogs was adequate, the carbohydrate given as the only other source of calories could be reduced to 25 calories per kilogram per day.

These references seem to offer the explanation for our inability to achieve an improved nitrogen balance by increasing the caloric intake with carbohydrate. For this purpose, it would be much more important to increase the nitrogen intake. This observation has considerable practical import, particularly to the surgeon attempting to maintain nitrogen equilibrium during periods of enforced postoperative starvation. The previous concept has led some surgeons to prescribe at least 4,000 c.c. of 10 per cent glucose daily, in order to provide the estimated minimal caloric intake deemed indispensable for nitrogen balance. Not only is this high volume of fluid believed to be unnecessary and undesirable for many patients, but, if protein and salt requirements are added to it, the administration of such large volumes of hypertonic fluids might well cause unfavorable local and systemic effects. The lowering of this estimated

caloric requirement to 25 calories per kilogram or less would be a boon to the problem of parenteral protein nutrition.

Our results—pronounced differences in positive nitrogen balance attained by oral in contrast to intravenous administration—differ from those reported by other investigators in man[18] and animal[19] for other casein digests. Brunschwig[18] reported that he could produce equally good nitrogen balance whether the proteins were fed by vein or by mouth; however, he used a casein digest intravenously and a natural whole protein orally. Cox[19] compared the same preparation given by both routes in dogs, but he used serum albumin regeneration as the criterion rather than nitrogen balance. In our studies, increases of serum proteins occurred too infrequently to utilize their measurements as a reliable index.

Madden and his co-workers[10, 20] however, are of the opinion that both the crystalline amino acids and the protein digests are better utilized orally than parenterally.

Previous work reported from this laboratory also substantiates the results reported here. In nitrogen balance studies with an oral lactalbumin digest,[11] an average retention of 43 per cent of the nitrogen administered was observed. This percentage was considerably in excess of that noted for two other casein digests administered intravenously.[13, 21] These observations are important enough to merit further study. If our findings are confirmed, more emphasis should be placed on the enteral protein feeding program. For this program, the protein would not have to be as completely digested; it would be less expensive to prepare and administer; it could be ingested in larger quantities; it would not have to be rendered pyrogen-free, and it could be used at home. The recent marketing of a number of protein digests for oral use bears testimony to the anticipated wider application of this method of feeding.

It has been observed that patients will refuse a meal offered during or immediately after an intravenous amino acid infusion. Symth and associates[22] studied the influence of two different protein digests on the voluntary intake of a 3,500 calorie diet, in seven patients. No significant effect was found in four patients given the amino acids orally, nor with the preparation which was a partial pork pancreas digest of casein. With a more complete acid digest of casein fortified with tryptophan, however, the depression of voluntary caloric intake exceeded the caloric gain from its administration.

In evaluating this phase of the study, we excluded the caloric value of the protein in the total intake; if we had included this, it would show that actually fewer than five patients had a significant decrease in caloric intake with increase in intravenous nitrogen administration. Considered along with the fact that fifteen of the twenty patients either remained the same or showed an increase in caloric consumption, this finding suggests that a revision of this clinical concept is in order. In practice, any slight objection to the use of amino acids intravenously is easily circumvented by giving the infusion after the noon meal (it being the largest meal of the day in most institutions) and giving an additional oral feeding before bedtime.

SUMMARY

1. When the basal caloric intake was 25 calories per kilogram per day or higher, increasing the caloric intake with carbohydrate was ineffective for improving nitrogen balance in five patients studied.

2. The oral administration of a lyophilized amino acid preparation produced a better nitrogen balance than its intravenous administration in seven of eight patients. With increased intake of protein, this difference was even more apparent.

3. The intravenous administration of increasing quantities of the lyophilized amino acid preparation did not consistently influence the voluntary intake of calories, principally that of carbohydrate. In the majority of instances, such intake either remained stationary or was improved.

We are indebted to Mrs. Irene Maxwell for the preparation of diets used in this study.

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INTRAPELVIC OBTURATOR NEURECTOMY FOR THE RELIEF OF CHRONIC ARTHRITIS OF THE HIP

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CHRONIC pain in the hip is almost entirely a condition of adult life and in the majority of instances is due to a chronic progressive degenerative hypertrophic arthritis (malum coxae senilis), which may or may not be secondary to some incongruity of the articular surfaces arising from a condition which began in early life, such as Legg-Perthes disease (osteochondritis deformans juvenilis) or a slipping of the proximal femoral epiphysis (adolescent coxa vara), or a congenital subluxation or dislocation of the hip. In other instances the pain is associated with a condition of more recent origin such as Paget's disease, aseptic necrosis following a fracture or dislocation of the hip, fracture of the acetabulum or of the femoral head, or an arthritis of the infectious or proliferative type.

In addition to the pain, which is aggravated by use and relieved by rest, the movements of the hip are limited to a variable degree, and the hip may be maintained in a position of deformity, especially adduction, flexion, and external rotation. It is thus evident that the patient may be seriously disabled. When confronted by a patient suffering from a condition of this type the experienced surgeon realizes that the hip is permanently damaged and that no form of treatment can be expected to restore the joint to a normal condition. He must decide whether to treat the hip conservatively or operatively.

Since operative attack on a painful hip is a formidable procedure with a result which is too often far from satisfactory, the surgeon tries conservative treatment first and finds that his most useful therapeutic agent is a crutch or a cane. This is combined with restriction of activity, reduction in weight, a low fat diet, vitamin B complex in relatively large doses, and thyroid or ovarian hormone when indicated. In patients with severe pain, rest in bed with or without traction may be indicated. We have tried deep x-ray therapy and large doses of vitamin D without appreciable therapeutic benefit.

Not infrequently the conservative treatment fails to afford relief or the patient rebels at prolonged and enforced inactivity and wishes that something more radical be done. In the past it was the custom to manipulate these hips under general anesthesia and then immobilize them in a large plaster cast in a position of abduction and internal rotation and extension. However, experience has shown that this rarely results in sufficient improvement to justify the procedure. Consequently, operative intervention is indicated.

As has been stated, the difficulty with operative intervention in these chronically painful hips is that the operation may prove formidable and may entail a long postoperative convalescence. This is especially true of an arthrodesis of the hip which is the only sure method of relieving the pain and maintaining ability to bear weight for a long time or walk a long distance. However, in these joints in which the articular surfaces are eburnated, arthrodesis is

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difficult to obtain and when successful the patient is handicapped by the loss of movement and may also be threatened by the possibility that the condition may involve the opposite hip. Consequently, arthrodesis has largely been abandoned by us in the treatment of these conditions.

We next consider an arthroplasty. This operation has been greatly improved by Smith-Petersen,[1] who interposes a Vitallium mold in the joint, but it is still a difficult procedure to perform satisfactorily and entails a prolonged convalescence. In our hands the results in these chronically painful hips leave a good deal to be desired. The hips are not infrequently unstable or painful or both, and the range of painless movement is usually not more than 50 per cent of normal.

Much the same may be said of the operation of cheilotomy. By this we mean the removal of the excess bone from the anterior and superior margins of the acetabulum and from around the articular margin of the head of the femur with or without the removal of diseased articular cartilage from both surfaces of the joint and the reduction in the size of the head of the femur (Murphy[2]). In some cases Smith-Petersen's[3] operation of acetabuloplasty which removes part of the anterior and superior portion of the acetabulum has given stable painless hips with a satisfactory range of movement. But this has occurred in the minority of our patients who have been operated upon by this method. We believe that the operation is most useful in those patients with an enlarged femoral head such as results from Legg-Perthes disease, and when combined with an obturator neurectomy.

A few years ago we were impressed with the reports of the benefits to be obtained in these patients by subtrochanteric osteotomy with inward displacement and outward angulation of the shaft on the proximal fragment of the femur. We performed a number of these subtrochanteric osteotomies on patients with chronic degenerative arthritis of the hip and most of the patients were improved (Key[4]). However, the operation entailed a prolonged convalescence and the degree of improvement was not as great as we had hoped for. So we are now performing the procedure less frequently than in the past.

For over fifteen years one of us (J. A. K.) has been performing extrapelvic section of the obturator nerves on an occasional patient with a chronic painful hip and has on several occasions combined this operation with an acetabuloplasty. Most of the patients were benefited, especially by the combined procedure; however, no accurate follow-up records on these patients are available.

The operation of intrapelvic obturator neurectomy has the advantages that it is a relatively short and simple operative procedure, once the technique of exposing the nerve has been mastered, and the convalescence from the operation is short. The technique of exposure of the nerves in the thigh was described by Stoeffel[5] in 1910 and the intrapelvic operation was described by Selig[6] in 1914. However, the operation is usually performed for relief of spasticity of the adductor muscles. We believe that this operation has been performed by many surgeons in this country for the relief of chronic pain and disability in the hip, but we were able to find no reports in the American or English literature on patients so treated.

Comitz[7] believed that the chief cause of pain and disability of the hip in arthritis deformans was the adduction contracture. He treated a series of such cases by section of the pectineus muscle and of both branches of the obturator nerve in the thigh. The operation was followed by prolonged physical therapy directed at improving the tone and power of the other muscles of the hip. This physical therapy was repeated annually in order to maintain function and postpone disability. He advised obturator neurectomy in the early stage of the disease and reported seven cases with satisfactory results. Blixenkrone-Moeller[8] reported on sixteen cases of chronic painful conditions of the hip in which the obturator nerve was sectioned inside of the pelvis by the method of Selig. In nine patients in whom there was true arthritis deformans and contracture of the adductor muscles, the results were good. But in seven cases of secondary arthritis deformans (Legg-Perthes disease and adolescent coxa vara) the results were poor. There was one death in his series from pulmonary embolism. He advised that the operation be performed only in patients with true arthritis deformans and with an adductor contracture.

Cottini[9] reported on sixteen patients with painful arthritis of the hip treated by Selig's intrapelvic obturator neurectomy and stated that the immediate results were good in all cases but that the arthritis was progressive and pain recurred in a moderate percentage of the patients.

There are also some reports of similar cases in the French literature and in these cases the operation was followed by improvement in gait and lessening of pain (Padonani,[10] Mallet-Guy and de Mourgeses,[11] and Santy, Berard, and Modnien[12]). Tavernier[13] preferred the less radical procedure of section of the deep branch of the nerve including the sensory articular twig, unless there is strong adductor contracture, as considerable disability may follow complete section of the nerve.

During the past eighteen months we have performed the operation of intrapelvic division of the obturator nerve in a series of twenty patients suffering from chronic painful conditions of the hip (Table I) and wish to report the results obtained in these cases.

The approach used was similar to that described by Selig. A vertical incision about 5 inches long is made in the lower abdominal wall along the lateral border of the rectus muscle. The lower end of the incision extends to the level of the pubic bone. The incision is carried through the superficial fascia and anterior sheath of the rectus and this muscle and the pyramidalis, if present, are retracted inward. With the fingers the areolar tissue and fat are stripped from the superior surface of the pubis, the fingers working outward and downward to the region of the obturator canal. The posterior sheath of the rectus is deficient in its lower portion. The intrapelvic opening of this canal is usually palpated without difficulty and then the finger is slipped outward and downward to palpate the obturator vessels and nerve. The pulsation of the artery can be felt and the nerve is hard, firm, and elastic and can be rolled against the wall of the pelvis in order that it may be identified. It has been said that it feels like a pencil, but it is not quite that large or hard. The head of the table is lowered and a large (1½ inch wide) ribbon or other suitable retractor is intro-

TABLE I

PATIENT, AGE, SEX	DURATION OF SYMPTOMS	DIAGNOSIS	PREVIOUS THERAPY	RESULTS AFTER OBTURATOR NEURECTOMY
C. A., 44, f	6 yr., severe disability; trouble with hip 23 yr.	Unknown etiology	Subtrochanteric osteotomy Oct. 46, no relief of pain	Complete relief of pain, but has difficulty in balance and complains of weakness in leg
D. H. K., 65, m	6 yr.	Malum coxae senilis, left hip	None	Complains of weakness and that leg gives out on use, but no gait disturbance and very little pain
E. Y. S., 42, m	12 yr.	Malum coxae senilis		Able to return to work; some weakness but no pain
C. M. C., 62, f	1 yr.	Malum coxae senilis, rt. hip	Appendectomy and repair of femoral hernia for this same pain	No relief of pain; no weakness or gait disturbance
I. W., 51, f	8 yr.	Malum coxae senilis, left hip	None	Pain less; walks better but unable to cross legs, while sitting
L. G. B., 64, m	3 yr.	Malum coxae senilis	None	No relief of pain, no change in gait
J. S., 65, m	6 yr.	Malum coxae senilis	None	Pain much less; some weakness and has some gait disturbance
A. T. S., 61, m	Arthritis for many years; inability to walk 14 days	Malum coxae senilis, both hips	None	Almost complete relief of pain, left leg weaker (leg weak before operation with atrophy of quadriceps); no pain in right unoperated hip
A. S., 25, m	12 yr.	Old slipped femoral epiphysis, rt. hip	Had nonoperative Rx. for slipping of epiphysis	Complete relief of pain; has trouble controlling leg in sitting position
E. M. B., 66, f	8 yr.	Traumatic arthritis following fracture, left hip	Conservative Rx	Relief of pain

duced into the wound in order to expose the nerve; with a small blunt dissector the obturator nerve is stripped from the surrounding tissues, care being taken not to injure the obturator vein or artery as this may cause troublesome bleeding and make visual identification of the nerve difficult. The nerve is then lifted up, grasped with a hemostat, and a section one or more inches long is excised. The wound is then closed in layers.

In adults the wound is about 4 or 5 inches deep and the nerve is farther lateral than one expects unless he had had experience with the operation. A good light should be directed obliquely downward and outward in the wound or an illuminated retractor may be used. In two bilateral cases we have used the transverse suprapubic (Pfannenstiel) incision, but we believe that a satisfactory exposure is a little more difficult by this method. With either type of incision, lowering of the head of the table is helpful as the abdominal contents then tend to fall away from the nerve.

In our series of twenty patients there were no complications, but we know of one case in which the painful hip followed a fracture of the pelvis and of

TABLE I—CONT'D

PATIENT, AGE, SEX	DURATION OF SYMPTOMS	DIAGNOSIS	PREVIOUS THERAPY	RESULTS AFTER OBTURATOR NEURECTOMY
J. W., 53, m	10 yr.	Traumatic arthritis secondary to fr. of hip	None	Improved but still has some pain; no gait disturbance
L. H., 42, m	3 yr.	Atrophic arthritis, both hips	None	Bilateral obturator section has improved motion, improved gait; pain much better but not completely relieved
N. M., 26, f	15 yr.	Arthritis rt. hip, secondary to pyogenic infection	14 operations on femur for osteo. from leg lengthening	Still some pain although considerably improved; walks better
F. T. G., 50, m	6 yr.	Old septic hip, right	None	Improved function of leg but feels he has about the same pain
M. A. W., 38, f	20 yr.	Old septic hip, right	None	Pain worse, has weakness and instability in leg; feels that she is worse than before operation
R. S., 59, m	5 yr., much worse last two yr., with shortening of leg	Paget's disease, left hip	Conservative treatment	Very little relief of pain, complain of weakness of leg with more trouble walking and controlling balance
K. H. K., 64, m	3 yr.	Paget's disease, right hip	None	Almost complete relief of pain but still pain at night; improvement in gait and ease of walking
J. Q. W., 16, m	5 yr.	Congenital subluxation, right hip	None	Pain much less; some loss of control in walking
M. V., 48, f	Congenital dislocation, pain, only 8 yr.	Congenital dislocation, both hips	None	Bilateral obturator section; pain in both hips on working but no pain when not working; no weakness or gait disturbance
M. B., 47 f	5 to 6 yr., pain worse since cup arthroplasty in 1945	Old hip fusion	Cup arthroplasty in Dec., 1945	Moderate relief of pain, leg is weaker and harder to control, but walks much better

the acetabulum. In this patient the obturator nerve could not be identified at the intrapelvic operation and the bladder was inadvertently opened. This was sutured and the patient made an uneventful convalescence, but the pain in the hip was not affected by the operation. In view of the experience in this case the surgeon should expect to encounter adhesions and distorted anatomy in patients who have suffered extensive fractures of the pelvis and of the acetabulum.

During the past one and one-half years we have performed the operation of intrapelvic section of one obturator nerve in eighteen patients and of both obturator nerves in two patients making a total of twenty-two sections in twenty patients and these patients have been observed for six months or longer. All of these patients were suffering from chronic painful conditions which affected one or both hips. In age they varied from a youth of 15 years suffering from a painful subluxation of the hip to patients over 60 years of age suffering from

Fig. 1 (A. S.).—Old slipped femoral epiphysis of right hip; almost complete relief of pain following intrapelvic obturator neurectomy.

Fig. 2 (J. Q. W.).—Congenital subluxation of right hip with pain on walking on five years' duration, improved after intrapelvic obturator neurectomy on the right.

Fig. 3 (E. M. B.).—Aseptic necrosis of left hip following fracture (eight years before); almost complete relief of pain following intrapelvic obturator neurectomy or the left.

malum coxae senilis. In one patient pain had been present for only one year, but in most of them pain had been present for from six to twenty years.

The diagnoses of these patients were as follows: malum coxae senilis, 7; old slipping of the femoral epiphysis, 2; traumatic arthritis following fracture of the hip, 2; proliferative arthritis both hips, 1; old pyogenic infection of the hip, 3; Paget's disease, 2; congenital subluxation of the hip, 1; congenital dislocation of both hips, 1; and a postoperative Vitallium cup arthroplasty, 1.

Fig. 4 (K. H. K.).—Paget's disease; pain in right hip following injury. Almost complete relief of pain following intrapelvic obturator neurectomy on the right.

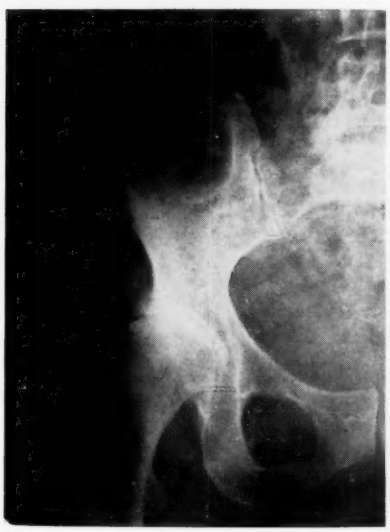

Fig. 5.

Fig. 6.

Fig. 5 (C. M. C.).—Early malum coxae senilis; pain not relieved after intrapelvic obturator neurectomy.

Fig. 6 (I. W.).—Malum coxae senilis. After obturator neurectomy pain was lessened but patient complained of some weakness and was unable to cross legs while sitting.

Regarding relief of pain, the results were in the main satisfactory. Three patients, one with Paget's disease, one with old pyogenic infection, and one with malum coxae senilis, complained that the pain was about the same as it was

before the operation and one patient with an old septic hip complained that the pain was worse than before the operation. The other sixteen patients obtained a variable degree of relief and in most of them the relief was so great that they are glad that they had the operation performed. In nine of these the pain was completely or almost completely relieved. In the other seven there was a variable amount of relief averaging about 50 per cent and in this group the function of the limb or limbs was improved to a variable degree.

In addition to the lessening of the pain the operation was in many patients followed by an increase in the range of movement in the hips and an improvement in the gait. Some patients, however, complained of weakness of the extremity, lack of endurance in walking, and difficulty in controlling the extremity, especially of inability to cross the operated leg over the other actively while sitting.

In reviewing these cases we find that the effect of the operation on the hip is not specific and cannot be predicted with certainty. For instance, two of our best results were obtained in the patients with old slipped femoral epiphysis. (These are the secondary arthritis deformans in which some other surgeons have obtained poor results.) The variation in the relief from pain obtained by the operation seems to be due in part to variation in the distribution of the nerve rather than to the lesion present. In our small series we were not able to determine that the operation is especially useful in any one type of chronically painful hip and that the results are apt to be unsatisfactory in any other similar condition.

The hip obtains sensory nerves from the obturator, femoral, and sciatic nerves and Eisler[14] stated that an accessory obturator is present in 29 per cent of individuals and that this carries sensory fibers to the hip. It is thus evident that section of the obturator nerve does not entirely denervate the hip. However, clinically we have found that the operation is followed by clinical improvement in 80 per cent of our patients.

How much of this improvement is due to paralysis or weakening of the adductor muscles we do not know. These muscles may receive some motor nerve fibers from the sciatic and some from the femoral nerve. Hence, the amount of paralysis of the adductors which will follow an intrapelvic section of the obturator nerve will vary in different patients and we know of no way in which this can be determined before the operation. We do not think that it is advisable to explore the sciatic and the femoral nerves at the primary operation in an attempt to denervate the hip completely.

Since the intrapelvic section of the obturator nerve may cause almost complete paralysis of the adductors and result in weakness, instability, and lack of endurance in the extremity, we believe that this operation should be reserved for those cases in which adductor spasm or contracture, or both, is judged to be a factor in the disability and that in most instances where an obturator neurectomy is to be performed the nerve should be exposed in the thigh at its exit from the canal and its deep or posterior branch and with it the sensory branch to the hip should be sectioned. This may or may not be combined with an acetabuloplasty. We are at present studying a series of cases operated upon in this manner.

In advising the operation of obturator neurectomy for the relief of a chronically painful condition of the hip, the surgeon should warn the patient that this is a palliative procedure and that it will not restore the hip to normal, but offers considerable lessening of the pain in about 80 per cent of the cases and that in most of these an appreciable improvement in the function of the hip may be expected.

CONCLUSION

Intrapelvic obturator neurectomy is a feasible and satisfactory surgical procedure for the relief of chronic painful conditions of the hip.

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A SIMPLE COMBINED APPROACH TO THE OBTURATOR AND FEMORAL NERVES

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IN THE course of treating patients with spasticity resulting from traumatic injury to the spinal cord, it was apparent that ambulation with braces and crutches was often thwarted by the presence of adduction spasm. Of a group of eight patients subjected to obturator neurectomy utilizing the approach described by Stoffel,[1] six were found to have been inadequately denervated. This technique requires extensive dissection of muscles and a careful search for and identification of the various branches of the nerve. Frequently, judging by my own experience, some of the more important branches are likely to be overlooked. In order to avoid this difficulty, I have sectioned the obturator nerve extraperitoneally above the pelvis, usually through a short Pfannenstiel incision. The results from this procedure have been uniformly good with respect to relief of adduction spasm. In patients so treated, ambulation could be pursued vigorously and adeptly. In observing attempts at ambulation in patients with severe flexion spasm in addition to adduction spasm, however, it became obvious that sharp flexion of the hip may also act as a serious impediment. In bed, such patients find it necessary to keep their legs tied down in order to prevent being thrown to the floor during sleep. In quadriplegic patients with this type of spasm, the inability to handle a urinal adds a grave problem. Abolition of flexion and adduction spasms allows the use of a urinal between the legs and often permits removal of an inlying urethral catheter and maintenance of a dry bed. To eliminate both flexion and adduction spasm, either section of the anterior spinal nerve roots[2] or peripheral section of the femoral and obturator nerves may be carried out.

The spasticity seen in the majority of patients with paraplegia with complete transverse lesions of the spinal cord is most frequently entirely flexor in nature with hip flexion and adduction of the thighs, flexion at the knees, and plantar flexion. With incomplete lesions (and occasionally in proved complete lesions) the spasm is largely extensor in nature, and is often associated with delayed flexor thrusts which may be spectacularly severe. These patients live in constant dread of being thrown from bed during sleep. They also find that the constant spasticity keeps them physically exhausted.

The attitude of watchful waiting in the hope of spontaneous improvement is mentioned only to condemn it; no cases of spasticity, even when followed as long as nineteen years after injury to the cord, have been observed to "wear

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out,'' except in the stages preceding death from sepsis. To be sure, many patients have been observed whose spasticity has diminished in about one year to the point where it no longer prevented the use of a wheel chair. Yet, many of these require treatment designed to diminish or abolish the frequent bouts of spasm. Some patients go for many hours without experiencing a single spastic movement, but have from time to time severe spastic episodes. Certainly these recurring uncontrolled movements deserve attention as much as any of severe motor ties occurring in otherwise normal people. Watchful waiting—or ''conservatism''—can only be branded as a policy of neglect. Tenotomy has not yielded as good results as nerve section and is not the procedure of choice.

Adduction is principally accomplished through the muscles innervated by the obturator nerve. The obturator nerve, a branch of the lumbosacral plexus with roots of origin in the ventral divisions of the second, third, and fourth lumbar nerves, emerges from the overlying psoas muscle over the sacroiliac joint. It courses along the lateral wall of the pelvis and enters the obturator canal. The obturator foramen is occupied largely by the two obturator muscles and is overlain by the parietal pelvic fascia. The obturator artery usually arises from the hypogastric artery and lies beneath the obturator nerve as these structures enter the obturator canal. Within the canal, the nerve divides into two branches. The anterior branch supplies the gracilis, adductor longus, and adductor brevis muscles. The posterior branch supplies the obturator externus and adductor magnus muscles. Occasionally, an accessory obturator nerve is present and supplies the pectineus muscle. The inferior portion of the adductor magnus muscle is supplied by the tibial nerve and functions chiefly in extension of the thigh.

Flexion of the thigh is largely subserved by the muscles innervated by the femoral nerve. The femoral nerve, with roots of origin from the dorsal division of the anterior primary division of the second, third, and fourth lumbar nerves, arises in the substance of the psoas muscle from the lower lateral border of which it emerges. It passes downward in the groove between the psoas and iliacus muscles to enter the thigh by passing beneath the inguinal ligament lateral to the femoral vessels and outside the femoral sheath. For the distance of approximately 1 cm. below the inguinal ligament, the nerve remains as a distinct bundle, then suddenly ends in profuse branching. Within the abdomen, branches are given off to the iliacus muscle and the femoral artery. In the thigh, the anterior division supplies the pectineus and sartorius muscles and gives off the medial and intermediate cutaneous femoral nerves. The posterior division supplies the quadriceps and gives off the saphenous and articular branches. Just above the inguinal ligament, the nerve is intimately associated with numerous blood vessels, making exposure difficult without extensive ligation of these.

In performing section of both nerves, a short skin incision is made starting 1 cm. above the inguinal ligament, midway between the anterosuperior spine and the symphysis pubis, and extending laterally and downward to a point 1 cm. lateral to the femoral artery and 1 cm. below the inguinal ligament (see Fig. 1).

The external oblique fascia is opened and the muscle is separated in the direction of its fibers. The contents of the inguinal canal are retracted medially and upward. The posterior wall is then pierced bluntly 1 cm. medial to the femoral vessels. The pelvic extraperitoneal space is thus entered and dissection is carried down bluntly to the obturator foramen. Here the nerve and artery can be palpated easily. The only precaution necessary is to avoid peeling off the parietal pelvic fascia along with the nerve and artery; this error makes the dissection difficult. Retractors are placed and the blood vessels and nerve are separated. The nerve is grasped with a hemostat or a nerve hook, silver clips

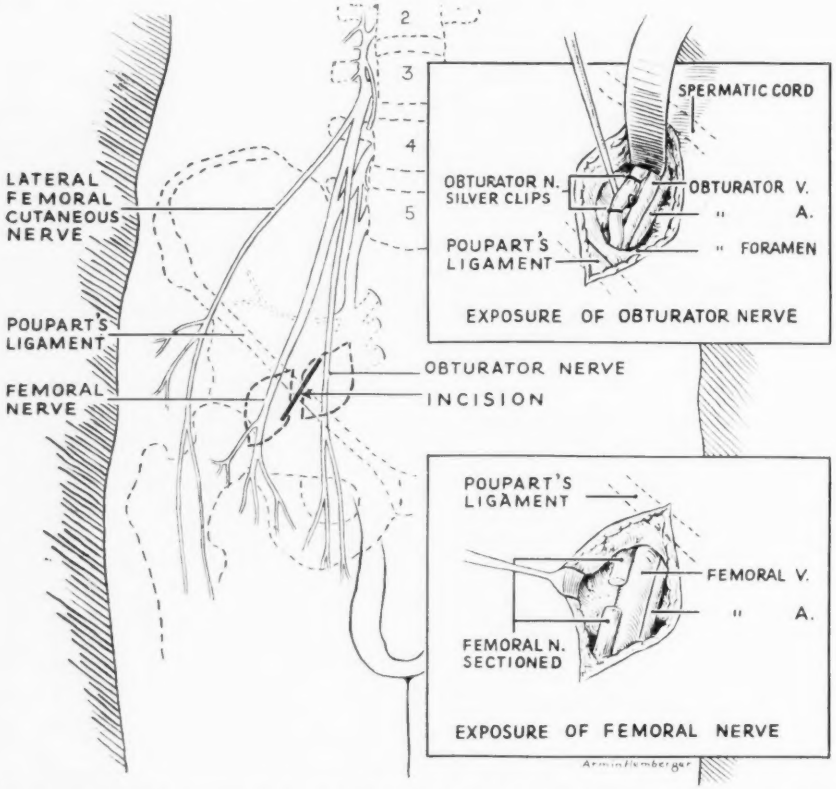

Fig. 1.—Combined approach to the obturator and femoral nerves. The skin incision is shifted to center, first over one nerve and then over the other. In the upper insert is shown diagrammatically the obturator structures, in the lower insert the femoral nerve and adjacent vessels.

are applied several centimeters apart, and a segment of nerve is removed. The stumps of the nerve are inspected for bleeding, since occasionally the small veins in and along the nerve are not occluded by the silver clips. The skin is then retracted laterally below the inguinal ligament and the superficial fascia is incised. The fascia overlying the iliopsoas muscle is split vertically 1 cm. lateral to the femoral canal. Directly beneath, the femoral nerve can be seen and picked up. Section can be accomplished with little or no bleeding, and by flexing the thigh, resuture can be done if desired.

The wounds are closed in layers with interrupted black silk sutures.

COMMENT

Because of the difficulties which follow incisions across natural skin folds and creases, it was originally felt wise not to place the incision across the flexor crease, but considerable difficulty was encountered with incisions placed either inferior or superior and parallel to it. Perhaps an incision along the inguinal crease extended superiorly at its mesial end and inferiorly at its lateral end would be suitable. At any rate, no annoying contractures or other difficulties have occurred in any of the patients operated upon with the incision used. Since the patients upon whom this operative procedure was used had complete anesthesia from the waist or higher, there was little need to consider the possible consequences of partial denervation of the hip and knee joints, nor of the cutaneous areas supplied. Despite the fact that the primary aim was to promote better ambulation, there was often a remarkable over-all improvement in general well-being. In some patients, bladder capacity improved markedly. In other patients who had incomplete spinal cord lesions, voluntary motion increased considerably. This improvement was probably due to the fact that the most severe aspects of the spasticity had merely kept the musculature from responding to voluntary stimuli. The inner surface of the thighs is one of the low threshold areas for eliciting spastic contractions, and once adduction is induced, other muscles which derive their innervation from segments of the spinal cord below the area of injury are reflexly stimulated (so-called "mass reflex"). With adduction being eliminated as a means of stimulating these sensitive skin areas, reflex actions are not started. Therefore, the other muscles remain relaxed for long enough periods of time to make them capable of responding to voluntary impulses which previously were unable to evoke responses because they were not as strong as the reflex action. In those patients where a suspicion exists that some voluntary motion may be present, resuture of the femoral at the time of its division is advisable.

SUMMARY

A simple method is described for the combined bilateral section of the obturator and femoral nerves for the adequate relief of flexion and adduction spasm in patients with paraplegia.

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EXPERIMENTAL STUDY OF WOUND HEALING

I. A New Technique and a Study of the Effect of Detergents and of an Antacid on Wound Healing

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A NONINFECTED wound of normal skin heals rather rapidly by contraction, tissue growth, and epithelization. With asepsis and protection of a standardized wound, healing time has been found to be quite constant.[1, 2] With topical application of certain drugs, the period of healing could be shortened by a few days[3] and the healed wounds seemed to have the same strength and appearance as the untreated ones. We felt that shortening of the healing process was desirable and that more drugs which would accelerate wound healing should be tested. We were interested to see also whether drugs used for the treatment of peptic ulcer would affect the healing of superficial skin wounds; lastly, we wanted to extend earlier work from this laboratory on the effect of detergents on wound healing, because promising clinical results had been obtained.[3]

In the healing of a wound of the skin, the processes of contraction, growth of fibrous tissue, and epithelization are apparent grossly. It is the impression of the surgeon, that usually the process of epithelization is more sensitive and more easily disturbed than the other two processes, and that it needs care and protection. For this reason we have devised a simple method which measures the rate of wound healing by epithelization, excluding largely the factor of contraction.

The number of drugs in use for wound healing is great, but the subject still is controversial. A number of such substances were shown to be ineffective, namely, chlorophyll, cod liver oil, vitamins A and D, balsam of Peru, various vitamins other than C and K, irradiated petrolatum, allantoin, chloramine, urea crystals, glycerin, pectin, biotin, Biodyne, urea, sulfathiazole, adenosine, and liver extracts.[4-6] Other substances were discovered to disturb wound healing, namely, sulfonamides, tannic acid, proflavine, hydrosulphosol, Biodyne, and Carbowax. Wounds dressed with petrolatum gauze and a stearate grease healed in the same time as controls.[7] Good results have been reported with the use of tissue extracts.[8, 9] In wound healing, maintenance or restoration of a normal metabolic and nutritional state of the body must never be forgotten.[10-14]

The method for wound healing used by Marshak[15] was tried and given up, because we could not duplicate some of his findings. Marshak covered a wound

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and surrounding skin with a methacrylate polymer in order to protect the wound, to prevent it from shrinking, and to be able to observe it through the film. We found it difficult to measure the rate of wound healing because the polymer obscured the wound and because a clouding exudate collected under the methacrylate film. Most importantly, methacrylate failed to prevent contraction of the wound and seemed to be irritating, causing in many cases fresh hemorrhage into the wound and irritation to the animals, for, although they were anesthetized, they immediately exhibited a protective motion with their limbs, as if trying to scratch the wound.

METHODS

Young guinea pigs of both sexes with an average weight of 250 grams were used. They were weighed before operation and every other day thereafter, until complete healing of the wounds. On the day before operation, the hair of the back, sides, and abdomen was cut with clippers, followed by a depilatory. Twenty-four hours later, the animals were anesthetized with sodium pentobarbital, 20 mg. per kilogram of body weight, intramuscularly. The skin was cleansed with soap and water, followed by iodine, alcohol, and ether. One wound was made on the saddle area of each flank, approximately 2 cm. lateral to the spinal column, by a stainless steel punch. The punch, ground at one end to a cutting edge, had an inner diameter of 11.5 mm.; it made a circular wound, measuring approximately 1.0 sq. cm. in area. The skin of the circular wound was dissected out with scissors, down to the subcutaneous layer, with little bleeding encountered usually. Then, after applying the agent to be tested to the wound, a Lucite ring was glued tightly to the skin surrounding the wound, using methacrylate polymer solution. The ring had a thickness of 1.5 mm., an inside diameter of 14 mm., and an outside diameter of 25 mm. Observations of the healing of wounds with and without the ring convinced us that it prevented wound contraction largely. The surface of the ring was covered by transparent x-ray film that was cemented to it with methacrylate polymer solution, serving as a window through which the rate of healing could be observed. The rings were re-enforced with adhesive tape in order to protect them from damage by the animals. The rings did not seem to disturb the guinea pigs.

The glue was prepared by dissolving isobutyl methacrylate polymer and methacrylate interpolymer,* 5 Gm. each, in 20 c.c. of methylethylketone; the solution was kept at 4° C.

The areas of the wounds were obtained by placing a piece of celluloid on the window and tracing the line of union between epithelial edge and granulating surface. Since the window was only 1 to 2 mm. above the wound, and since the margins of the ingrowing epithelium could be distinguished easily, the outlines could be traced accurately. The area of the tracing was measured with a planimeter, according to the technique of Carrell.[1] Wound healing is expressed as the size of the healed area in per cent of the original wound. A few wounds showed slight initial enlargement.

*We are indebted to E. J. DuPont de Nemours Company, Wilmington, Del. for the polymers.

The different series of experiments performed were compared for statistically significant differences by the chi square test (Fisher), using a 5 per cent level of significance. Under results, we refer to this analysis, when differences are called statistically significant. Most reliance was placed on the proportion of animals showing 80 per cent healing of the wounds on the eighth day for the following reasons: healing was definitely progressive on that date; when the results were compared it became evident that on the eighth day differences between the series of experiments were most pronounced; when certain drugs obscured the wounds so that daily readings of the rate of healing could not be obtained, the windows over the wounds had to be removed; since this could not be done repeatedly without disturbance of the wounds, it was convenient to choose the eighth day for removal.

EXPERIMENTS

The detergents used were of the anionic, cationic, and nonionic type, with sodium lauryl sulfate (Dreft), tetramethylammonium-hydroxide (Triton NE), and alkyl-dimethyl-benzyl-ammonium-chloride (Zephiran), chosen from each category. The antacid was a sodium carboxymethylcellulose developed in this laboratory, and was used alone or in combination with magnesium oxide, sodium bicarbonate, and sodium lauryl sulfate.

The rate of healing of control wounds was found to be the same, whether an animal had an untreated wound on one flank and a treated faster healing wound on the other flank, or whether both wounds were treated or untreated. This showed that the healing process of one wound did not influence that of the contralateral side.[4]

Wounds with low-grade infections healed as well as clean, noninfected wounds.[4] Animals with distinctly infected wounds were discarded. Untreated controls were run throughout the duration of this work, in order to eliminate possible changes in rate of healing due to extraneous factors, or due to nutritional deficiencies. All animals were fed the some diet of cabbage, lettuce, alfalfa, and oats. Following complete healing of the wounds, the animals were etherized and exsanguinated, and hemoglobin, red blood cell count, and total proteins were determined. After observing wound healing in Controls A and B and after having observed five animals not operated on, but shaved, given anesthesia, weighed, and fed the same as the operated animals, it was found that variations in body weight, red blood cells, hemoglobin, and total proteins were insignificant.

RESULTS

The average rate of healing of untreated control wounds (Table I, Controls A and B) was inconsistent during the first six postoperative days in so far that a progressive process of healing was not evident. At the seventh to eighth day, this inconsistency disappeared and healing became progressive. This is demonstrated by Controls A which, on the fourth postoperative day, showed an average rate of healing of only 16.6 per cent with a variation of –28.6 to 50 per cent; no significant increase in the rate of healing was noted until the eighth postoperative day.

TABLE I. AVERAGE PERCENTAGE RATE OF HEALING WITH VARIOUS DETERGENTS

TYPE OF AGENT	NO. OF WOUNDS	PER CENT RATE OF HEALING OVER NUMBER OF WOUNDS HEALED COMPLETELY (POSTOPERATIVE DAYS)													AVERAGE NO. DAYS FOR 100% HEALING
		1	2	3	4	5	6	7	8	9	10	11	12	13	
A. Control	24	11.1-0	15-0	14.5-0	16.6-0	-0	29-0	36.4-0	51-1	70.2-0	78.9-1	90.7-8	99.9-13	100-1	11.6
B. Control with 2% methylcellulose	11	3-0	9-0	11-0	18-0	29-0	24-0	31-0	46-0	53-0	64.0	92-4	100-6	100-1	11.7
C. 1% sodium lauryl sulfate in H_2O	21	-.9-0	3.8-0	10.7-0	10-0	16.8-0	34.3-0	47.5-0	56.1-0	68-0	89.7-2	99.1-17	100-2		11.0
D. 1% sodium lauryl sulfate in ointment	8	-6.3-0	4.7-0	9.4-0	4.2-0	20-0	33.3-0	39.8-0	68.5-0	73.8-0	91.4-1	100-7			10.9
E. 1% sodium lauryl sulfate in methylcellulose	4	-11-0	12.1-0	3.8-0		54.8-0	66.4-0		81.3-0	97.6-3	100-1				9.2
F. 2% sodium lauryl sulfate in methylcellulose	10	8.2-0	12.3-0	23.4-0	28.4-0	53.9-0	59.3-0	82.9-0	93.6-5	100-5					8.5
G. 1% tetramethylammonium hydroxide in methylcellulose	4	4.3-0		16.3-0	17.4-0		35.8-0	57.9-0	71.5-0	75.8-0	87.7-2	97.8-1	100-1		11.2
H. 1.28% alkyl-dimethyl-benzyl-ammonium-chloride in methylcellulose	3	6.1-0		30.1-0	36.8-0	28.7-0	31.3-0	33.9-0	66.9-0		93.6-1	100-2			10.7

In Controls A and B, Table I, the average time of complete healing was 11.6 and 11.7 days, respectively, and 80 per cent healing was observed in both on the tenth to eleventh day. There was not statistically significant difference between Controls A and B.

In Control A the wounds were untreated, while in Control B, 2 per cent methylcellulose solution was applied to the wounds. This solution was selected as a base for drugs for its low absorbability and its transparency, and for staying in contact with a wound for a relatively long period of time. Aquaphor ointment base (U.S.P. ointment No. 11) was found unsatisfactory, because it concealed the wounds. The use of water as a solvent was unsatisfactory, as absorption and evaporation of the water could not be controlled. After one series with a single application of 1 per cent sodium lauryl sulfat in water, another series was performed with re-instillation of the watery solution through the window every other day. Since the results were practically the same, they were added together as Series C, which was not significantly different from the controls. Neither did 1 per cent sodium lauryl sulfate in Aquaphor ointment show a pronounced effect on healing (series D).

Series E, with 1 per cent sodium lauryl sulfate in methylcellulose, showed complete healing in 9.2 days and 80 per cent healing in 8 days. The statistically most significant increase in the rate of healing with detergents was noted in Series F, using 2 per cent sodium lauryl sulfate in methylcellulose, with 100 per cent healing in 8.5 days and 80 per cent healing in 7 days. Tetramethylammonium-hydroxide (Series G) and alkyl-dimethyl-benzyl-ammonium-chloride (Series H), both in methylcellulose, did not show significant effects on healing rate.

On studying the average percentage rate of healing with antacids (Table II), it was found difficult to measure the size of the wounds every day, because the antacid solutions or suspensions were cloudy. Therefore, the degree of healing was determined on the eighth day.

In Series I (sodium carboxymethylcellulose) an additional control was run with an untreated wound on one side of the animal and 3 drops of a 1.8 per cent sodium carboxymethylcellulose solution on the other in order to determine whether a gradual improvement of our operative technique might have changed the rate of healing of untreated wounds. It was found that this was not the

TABLE II. AVERAGE PERCENTAGE RATE OF HEALING WITH ANTACIDS

TYPE OF AGENT	NO. OF WOUNDS	PER CENT RATE OF HEALING OVER NUMBER OF WOUNDS HEALED COMPLETELY (POSTOPERATIVE DAYS)					
		8	9	10	11	12	13
I. 1.8% sodium carboxymethyl-cellulose	5	90-0	100-5				
J. 1.8% sodium carboxymethyl-cellulose, 0.6% magnesium oxide	10	93.5-3	100-7				
K. 1.9% sodium carboxymethyl-cellulose, 0.23% sodium bicarbonate, 0.23% sodium lauryl sulfate	10	81.5-0	99.2-10				
A. Control	24	51-0	70.2-0	78.9-1	90.7-8	99.9-13	100-1

case. The sodium carboxymethylcellulose increased the rate of healing significantly, with 100 per cent healing of all animals on the ninth postoperative day and 80 per cent healing before the eighth day. Series J (sodium carboxymethylcellulose and magnesium oxide) and K (sodium carboxymethylcellulose, sodium bicarbonate, and magnesium oxide), also displayed marked increases in the rate of healing over Controls A and B. In Series J, 100 per cent healing of the animals occurred in 8.7 days, and 80 per cent before the eighth day. In Series K, 100 per cent healing occurred on the ninth day and 80 per cent on the eighth day. Statistically, there was no significant difference between the effects of the different antacids, but we feel that Series J with 1.8 per cent carboxymethylcellulose and 0.6 per cent magnesium oxide gave the best results.

A summary of all results on the eighth day is presented in Table III. The spread in the range of the rate of healing is presented in the first column; it was wide in the controls and with 1 per cent sodium lauryl sulfate in water or in ointment, and it was distinctly smaller, that is, healing was more uniform, with all detergents and with all antacids in methylcellulose.

The mean rate of healing (Column 2) was high, that is, above 80 per cent, for 1 per cent and 2 per cent sodium lauryl sulfate in methylcellulose and for all three antacids.

In the case of 2 per cent sodium lauryl sulfate in methylcellulose the data are even better than apparent in Table III, because 80 per cent healing was attained on the seventh day already; likewise, in the case of the antacids, healing on the eighth day was well above 80 per cent in Series I and J. In Experiment J, the wounds were measured on the seventh day (not on Table III) and showed

TABLE III. PERCENTAGE OF HEALING ON EIGHTH DAY

PROCEDURE	1 RANGE OF PER CENT HEALING	2 MEAN OF PER CENT HEALING	3 NO. OF WOUNDS WITH 80 PER CENT OR MORE HEALING OVER TOTAL NO. OF WOUNDS	4 NO. OF WOUNDS WITH 100 PER CENT HEALING
A. Control	22-100	51.0	1/24	1
B. Control with methylcellulose	19-70.3	46.0	0/11	0
C. 1% sodium lauryl sulfate in H_2O	20-83	56.1	0/21	0
D. 1% sodium lauryl sulfate in ointment	37-70	68.5	0/28	0
E. 1% sodium lauryl sulfate in methylcellulose	70.6-90	81.3	4/ 4	0
F. 2% sodium lauryl sulfate in methylcellulose	66.6-94	93.6	5/10	5
G. 1% tetramethlyammonium-hydroxide in methylcellulose	68.7-77.7	71.5	0/ 4	0
H. 1.28% alkyl-dimethyl-benzyl-ammonium-chloride in methylcellulose	64-70	66.9	0/ 3	0
I. 1.8% sodium carboxymethylcellulose	77-98	90.0	5/ 5	0
J. 1.8% sodium carboxymethylcellulose, 0.6% magnesium oxide	80-100	93.5	3/10	3
K. 1.9% sodium carboxymethylcellulose, 0.23% sodium bicarbonate, 0.23% sodium lauryl sulfate	70-90	81.5	8/10	0

90 per cent healing already. Although statistically there was no significant difference between the effects of the various detergents, we feel that 2 per cent sodium lauryl sulfate in methylcellulose was the best combination. There is no significant difference between the results with 2 per cent sodium lauryl sulfate (Series F) and 1.8 per cent sodium carboxymethylcellulose with 0.6 per cent magnesium oxide, both in methylcellulose base.

DISCUSSION

According to Hartwell,[16] epithelization takes place through ameboid movement into the wound of epithelial cells from the surrounding epithelium. Epithelization is completed by union of extension membranes growing from the edges of the wounds. According to Hartwell, the formation of such membranes is dependent on the presence of a supporting base, suitable for epithelial cell movement. This base is a factor for the support and advance and for the time of union of the epithelium from the edges of a wound. The presence of an unsuitable base is probably one of the causes of delayed wound healing, and it may be responsible in part for the formation of "indolent" wounds.[17]

Another factor in wound healing is pH. Heterolysis seems to depend mainly on action of leucocytic enzymes which, at alkaline reaction, digest dead tissue, but which do not attack living cells or unchanged connective tissue fibers. This heterolysis of dead tissue permits the removal of barriers of dead tissue to the extension membrane and allows for the ameboid activity of the epithelial cell. Messer and McClellan[18] found that wounds benefited more from an alkaline pH than from an acid one, but we are aware of evidence that acidity, or a pH between 6 and 8, is favorable to wound healing.[19]

The significantly increased rate of epithelial healing, seen in our experiments with the detergent sodium lauryl sulfate in methylcellulose base, can be attributed in part to its alkaline reaction, and to its spreading by lowering surface tension. The methylcellulose, which is inert, serves as a base for keeping the detergent in moist contact with the wound for a sufficient period of time, and it may constitute a supporting base suitable for epithelial cell movement, which helps the expansion of the epithelial membrane. The effect of lowered surface tension by itself on wound healing is unknown, but it may play a role in the process of ameboid epithelization.

The significantly increased rate of healing seen in our experiments with sodium carboxymethylcellulose alone, with sodium carboxymethylcellulose plus 0.6 per cent magnesium oxide, and with sodium carboxymethylcellulose with 0.23 per cent sodium lauryl sulfate and 0.23 per cent sodium bicarbonate may be attributed to the two factors just mentioned. First, these substances give an alkaline pH, and second, carboxymethylcellulose itself may have served as a supporting base.

These studies are continued with sodium carboxymethylcellulose in patients with peptic ulcer, and with antireticulocytic serum on wound healing in guinea pigs.

SUMMARY

A simple technique is described for the study of the epithelization phase of wound healing with which the contraction phase of healing is eliminated largely.

Sodium lauryl sulfate and sodium carboxymethylcellulose, a new antacid, in a methylcellulose base showed a significant increase in the rate of healing.

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THE EFFECTIVENESS OF DRUGS IN PREVENTING POSTOPERATIVE PENILE ERECTIONS

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THE pain, wound separation, and hemorrhage occasionally seen in patients undergoing penile surgery are disconcerting complications to both patient and surgeon. If erections could be stopped or diminished during the immediate postoperative period, these complications could be reduced to a minimum. When this study was begun a review of the literature covering the past ten years showed but a single reference to this subject, Christopher's[1] recommendation to use sodium bromide.

METHOD

In conducting this study it was decided to evaluate the effectiveness of sodium bromide, oral diethylstilbestrol, and hypodermic estrone on young male patients who were to have circumcisions. This work was done at an Army Station Hospital located at a Port of Embarkation. The patients used in the study were enlisted Army personnel. All patients were hospitalized to allow for close observation, daily recording, and strict control in the administration of the appropriate drugs.

Patients were admitted to the hospital the day before surgery, and were not discharged until the fifth postoperative day or later. We carefully interviewed each patient daily as to the number, severity, and duration of penile erections during the preceding twenty-four hours. The results were tabulated on master charts. All surgical complications were noted and recorded. The patient's age, weight, race, degree of phimosis, and emotional status were charted.

The operative procedure for circumcision was standardized by us to obtain further uniformity. The method advocated by Pugh,[2] Orr,[3] and Christopher[1] was used in this series of cases. Anesthesia was obtained by dorsal nerve block with 1 per cent procaine, and local infiltration when necessary. A few patients were given a caudal block type of anesthesia (30 c.c. of 2 per cent procaine). In this series no dressings were used, the patients being instructed to sponge the wound with tepid boric acid solution every thirty to sixty minutes during the day of operation. This usually resulted in a dry and painless wound after a few hours.

A total of 157 circumcisions were done by us in this series. Reported here are 125 of these cases, divided into five study groups. The remaining 32 cases were eliminated from the series because of missed medications or incomplete follow-ups.

We originally divided our cases into four groups of twenty-five patients each. Patients were assigned at random to the various study groups. Group

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one consisted of twenty-five patients who were used as the control group. These patients received no medication other than an occasional 5 gr. of Aspirin. The second group of patients were given oral diethylstilbestrol* in a dosage of 5 mg. the afternoon before surgery, and then 5 mg. twice daily through the fifth or sixth postoperative day. Sodium bromide in onset dose of 2 Gm. the afternoon before operation, and 1 Gm. three times daily thereafter, was given to patients in the third group. The fourth group was treated by hypodermic injections of estrogen* once daily (1 mg. or 10,000 units of Estrone*) beginning on the day before surgery.

After the completion of this study our attention was drawn to a recent report by Higgins[4] in which he recommended the preoperative use of stilbestrol in young hypospadius patients until they are "unable to have an erection." Accordingly, we added a fifth group of twenty-five patients to our series, giving them 5 mg. of stilbestrol twice daily for three to seven days before surgery, and continuing until the fifth postoperative day.

RESULTS

Out of the 125 patients reported here, in five equal groups, the number of erections per patient for a five-day period, starting with the day of surgery and continuing through the fourth postoperative day, varied from 0 to 19, with a mean average of 5.18 erections per patient. Table I compares the total number and average number of erections in the five groups.

TABLE I

	GROUP	TOTAL NUMBER OF ERECTIONS FOR FIVE-DAY PERIOD	PERCENTAGE AS COMPARED TO CONTROL GROUP	AVERAGE NUMBER ERECTIONS PER MAN PER DAY
I	Control	179	100	1.43
II	Diethylstilbestrol (started the afternoon before surgery)	135	75	1.08
III	Sodium bromide	128	71	1.02
IV	Estrone	152	84	1.21
V	Diethylstilbestrol (started at least three days preoperatively)	56	31	0.44

It is readily apparent that the patients receiving oral diethylstilbestrol several days preoperatively had a great diminution in the number of erections as compared to the patients in the other groups.

The age (16 to 30 years), weight (125 to 225 pounds), or race of the patient seemed to have little relationship to the frequency of erections. The patients classified as having a nervous emotional status had the greatest number of erections (Table II).

TABLE II

EMOTIONAL STATUS	NUMBER OF PATIENTS	AVERAGE NUMBER OF ERECTIONS FOR FIVE DAYS
Nervous	17	6.9
Normal	101	5.8
Lethargic	7	4.4

*Supplied by Abbott Laboratories, North Chicago, Ill.

Complications encountered in the 157 cases of circumcisions were on the whole minimal. Of thirty patients given bromides, one had nausea and three had nausea and vomiting (one of which had such severe vomiting that the drug was discontinued). Only one of the fifty-eight patients given oral diethylstilbestrol had nausea. The high incidence[5] of gastric reactions reported in other series of stilbestrol therapy was not substantiated in this group of male adults on relatively large doses (10 mg. daily).

There were five cases with mild postoperative bleeding from the circumcision wound, and two with severe bleeding, necessitating ligation of the bleeders. One patient had a severe wound separation about ten days postoperatively, due to frequent and intense erections which came on after the stilbestrol therapy had been discontinued on the seventh postoperative day. Two other patients had small, partial wound separations. One patient had a persistent subcutaneous infection of the penis manifested by pain, tenderness, and edema that required incision and drainage on the ninth postoperative day.

CONCLUSIONS

1. Postoperative comfort can be improved, and complications reduced in patients undergoing circumcision by minimizing erections with the use of adequate pre- and postoperative stilbestrol therapy.

2. In plastic operations or amputations of the penis, prophylactic stilbestrol therapy to minimize erections would seem to be particularly indicated.

ADDENDUM

Since the completion of this study, Vermooten[6] published a report which presented his results in controlling postoperative penile erections with stilbestrol. His experiences showed dosages of 4 mg. daily controlled 50 per cent of erections, and dosages of 6 mg. daily controlled 72 per cent of erections. (Erections were classified as uncontrolled if the patient had an average of one or more erections per twenty-four hours for the five-day period.)

In our series the patients who received 5 mg. of stilbestrol twice daily, beginning the evening before surgery, had 75 per cent as many erections as the control group. Those receiving stilbestrol, 5 mg. twice daily for at least three days preoperatively, had only 31 per cent as many erections as the control group.

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BENIGN ADENOMA OF THE LIVER

Successful Surgical Resection of Tumor Involving Both Right and Left Lobes

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DESPITE the uncommon occurrence of primary neoplasms of the liver, a relatively large number of instances of surgical resections of hepatic tumors has been reported. Most of these have been resections of tumors of the left lobe or lesions with a pedunculated attachment. We have recently had an opportunity to remove successfully a large sessile liver-cell adenoma which involved the right hepatic lobe and extended into the left lobe.

CASE REPORT

R. H. (No. 393083), a 27-year-old white housewife, was admitted to the Johns Hopkins Hospital on Oct. 12, 1946, because of pain in the right upper quadrant of the abdomen of seven years' duration. The patient had been healthy all of her life until seven years before admission when there developed the first of a series of episodes of pain in the right upper quadrant. These attacks usually came on suddenly, lasted for twelve to forty-eight hours, and were associated with nausea, and occasionally vomiting. The pain frequently radiated through to the back. There was never any jaundice, clay-colored stools, indigestion, or intolerance of fatty foods. These episodes occurred every three to five weeks. In 1941 exploratory laparotomy was performed at another hospital, after which the patient was told she had cancer of the liver. The condition remained unchanged after this operation and she continued to have attacks of pain every few weeks. In 1943 she went through a normal pregnancy and a normal child was delivered at term. In January, 1946, because of continued episodes of pain and vomiting, a second laparotomy was carried out in another hospital at which time the liver was found to be "hypertrophied" and the gall bladder filled with stones. Cholecystotomy with removal of stones and biopsy of the liver were done. The pathologic report on this occasion showed no evidence of carcinoma and a diagnosis of "hepatitis" was made. Following this procedure there was a remission of symptoms for two months. The attacks of pain and vomiting then recurred and became increasingly frequent and more severe in the three months before admission to the Johns Hopkins Hospital. The patient had been aware of a mass in the right upper quadrant of the abdomen since shortly after the first operation in 1941, and in the year prior to admission to this hospital this mass had increased greatly in size. Weight had increased about forty pounds during the seven-year period of symptoms.

On physical examination the temperature was 98.6° F., pulse 80, respirations were 18, and blood pressure was 124/68. The patient was a well-developed, moderately obese, young white woman in no distress. Positive findings were limited to the examination of the abdomen. There were well-healed right rectus and right subcostal operative scars without hernias. A firm, nontender, rounded mass was palpable in the right upper abdomen extending from the costal border down to the level of the umbilicus and laterally well back into the right flank. The spleen was not palpable. There was no evidence of ascites and no dilated abdominal veins. Pelvic and rectal examinations disclosed no abnormalities.

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Laboratory Studies.—The urine was negative, the hemoglobin was 13 Gm. per cent, and the leucocyte count was 8,200 with normal smear. Serologic test for syphilis was negative. Further blood studies showed nonprotein nitrogen 31 mg. per cent; fasting blood sugar 88 mg. per cent; chlorides 105 meq. per liter; CO_2 combining power 27 meq. per liter; bilirubin less than 0.8 mg. per cent; amylase 73 mg. per cent reducing substance; alkaline phosphatase activity 5.0 Bodansky units; serum protein 7.8 Gm. per cent with albumin 5.1 Gm. per cent, and globulin 2.7 Gm. per cent. Liver function tests showed bromsulfalein 0.9 mg. per cent retention per 30 minutes; hippuric acid 0.15 Gm. excreted in one hour; cephalin flocculation negative; thymol turbidity 8.3 units.

A roentgenogram of the chest showed no abnormalities. On x-ray examination of the abdomen after the ingestion of a barium meal there was seen a large rounded shadow in the right upper quadrant with marked displacement of the stomach and duodenum to the left (Fig. 1). Intravenous pyelograms showed the kidneys to be normal in size, shape, and position. There was no displacement of the right kidney by the mass which lay anterior to it. On cholecystography there was no concentration of the dye in the gall bladder.

The preoperative diagnoses were hepatomegaly of unknown etiology, possible benign tumor of liver; chronic cholecystitis and cholelithiasis.

Fig. 1.—Roentgenogram of abdomen after barium meal showing displacement of stomach and duodenum to left by hepatic tumor in right lobe of liver (indicated by arrows).

Operation (W.P.L.).—Under gas-oxygen-ether anesthesia a right subcostal incision was placed and the peritoneal cavity entered. There were dense vascular adhesions between the omentum, the anterior abdominal wall, and a large rounded tumor which extended from the lower border of the right lobe of the liver. The omental attachments to the tumor were divided and the hepatic flexure of the colon was mobilized. A specimen of the tumor was obtained for biopsy and the report on the frozen section was "liver-cell adenoma." By extending the subcostal incision across the midline and by dividing the falciform ligament, adequate exposure of the tumor was obtained. This was about six inches in diameter, well

encapsulated, and arose from the anteroinferior aspect of the liver; about three-quarters of the mass lay in the right lobe and the remaining one-quarter of the mass extended across into the left lobe (Fig. 2). By elevating the tumor the gall bladder and the hepatic hilum were exposed lying just posterior and inferior to the lowermost line of attachment of the tumor. By traction downward on the tumor the uppermost border could be visualized. After complete freeing of the tumor and adjacent liver of all adhesions to the anterior and lateral abdominal parietes, the resection of the tumor was begun by first placing and tying a double row of mattress sutures of 0 silk through the full thickness of the liver at the margin of the tumor on the right and dividing the liver substance with the knife between these sutures. By advancing along the margin of the tumor in this manner, the operator was able to control bleeding without undue difficulty. After the right half of the tumor had been freed by this method it seemed advantageous to begin the resection in the same way on the left

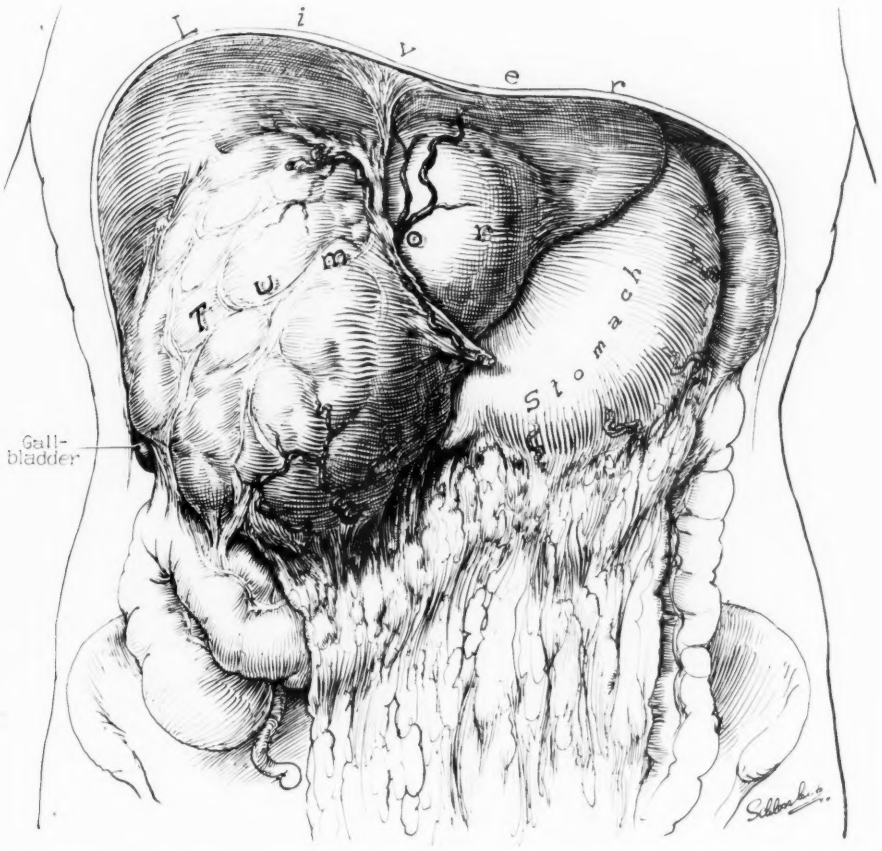

Fig. 2.—Sketch illustrating position and relations of benign hepatic cell adenoma in patient R.H.

and advance to the right until the tumor was completely removed intact along with a narrow margin of normal liver tissue. Traction on the tumor greatly facilitated the placing of sutures, and the exposure of the liver hilum by this maneuver repeatedly avoided injury to the external biliary ducts. The gall bladder, which lay at the edge of the lower margin of the line of resection, was atrophic and a stone was impacted in the cystic duct. The gall bladder was removed. The common duct was not dilated and no injury to the structures in the hepatic hilum had been inflicted by resecting the large tumor. Several pieces of gelatin sponge were placed over the raw surface of the liver to control superficial ooze

and the omentum was brought up over this area. A cigarette drain was placed to Morison's pouch and the abdominal incision then closed in layers with interrupted silk sutures.

Course.—The patient received a total of 3,000 c.c. of whole blood during the operative procedure and in the immediate postoperative period. She had low-grade fever for the first few days after operation but then remained afebrile. Penicillin in doses of 320,000 units daily was given for ten days. She was maintained on a high carbohydrate, low fat diet. The drain was mobilized slowly and was not completely removed until the tenth postoperative day. The wound healed per primam and recovery was uneventful.

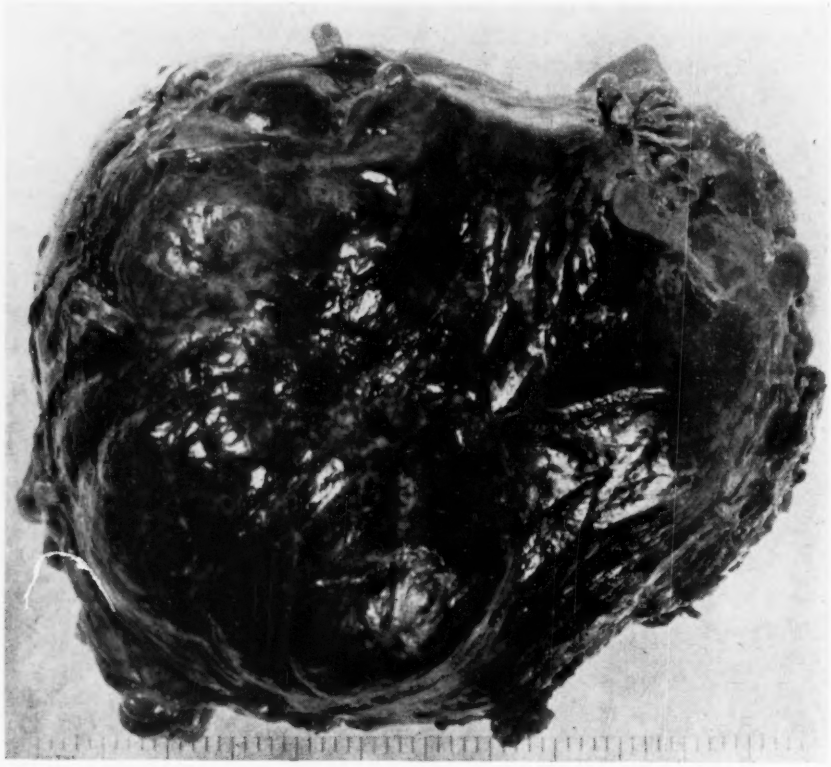

Fig. 3.—Photograph of surgically resected hepatic tumor (R.H.); weight 925 Gm.

On the eighth postoperative day blood studies were repeated with the following results: nonprotein nitrogen 28 mg. per cent; fasting blood sugar 88 mg. per cent; chlorides 103 meq. per liter; CO_2 combining power 24.2 meq. per liter; bilirubin 0.6 mg. per cent; serum protein 7.3 Gm. per cent with albumin 4.4 Gm. per cent and globulin 2.9 Gm. per cent; serum amylase 125 mg. per cent reducing substance; cholesterol 152 mg. per cent; alkaline phosphatase activity 4.3 Bodansky units. Liver function tests were repeated and showed: bromsulfalein 2.2 mg. per cent retention in 30 minutes; hippuric acid 0.55 Gm. excreted in one hour; cephalin flocculation was negative, and thymol turbidity 2.7.

The patient was discharged on the twelfth postoperative day. She has been followed for twelve months in the outpatient department and remains in good health with no evidence of recurrence of the tumor and no sign of hepatic damage.

*Pathologic Examination.**—The specimen consisted of an encapsulated mass measuring 15 by 12 by 7 cm. and weighing 925 Gm. (Fig. 3). The mass was quite firm. The capsule was roughened by adhesions in numerous areas but was intact except at the site of biopsy.

*By Dr. Mitchell Miller.

On section the cut surface was tan in color and resembled liver. There was no bile staining. No areas of necrosis were found and nowhere did the capsule appear to be invaded.

On microscopic examination of sections from different parts of the tumor a similar histologic picture was seen. There was a delicate fibrous capsule, which was scarred in areas. The parenchyma was composed of almost normal-appearing liver tissue with polygonal cells resembling normal hepatic cells (Fig. 4). The cells formed cords which anastomosed with one another, leaving sinusoidal endothelial-lined spaces between them. No accumulations of bile pigment were seen in any of the sections. Central veins were seen in some areas and portal areas were quite evident, but bile ducts were conspicuously absent. The parenchymal cells were regular in size with no hyperchromatism, and no mitotic figures were seen. There was no invasion of the capsule.

Diagnosis.—Adenoma of liver, hepatic cell type.

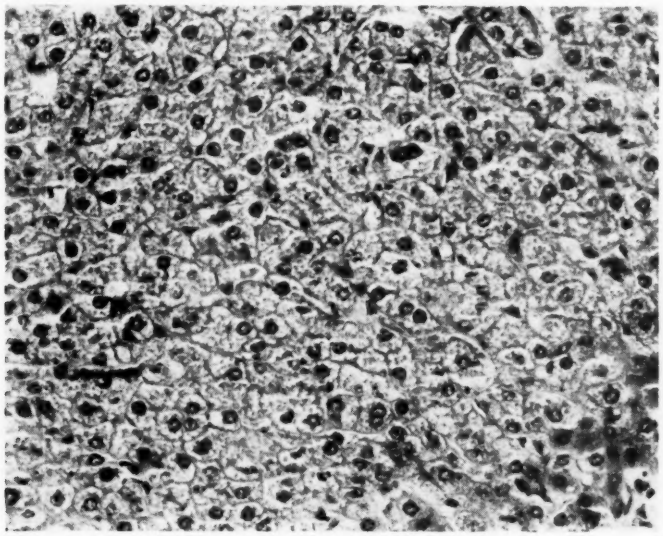

Fig. 4.—Photomicrograph (×350) to show histologic detail in benign adenoma of liver (R.H.)

COMMENT

In recent years there has been increasing interest in surgical resections of tumors of the liver. In this clinic Shumacker[1] in 1942 successfully removed an angioma of the left lobe, and Pickrell and Clay[2] in 1944 developed a technique for total left lobectomy of the liver, applying it successfully in three cases.

Warvi[3] in 1945 found thirty-three instances of resection of solid adenoma of the liver in the world literature with a postoperative mortality of 9 per cent. He added three cases from the Cincinnati General Hospital. Hershey[4] reported a case in 1946, and in 1947 two additional cases were reported by Duckett and Montgomery.[5]

Earlier reports are concerned chiefly with wedge-resection of tumors of the left lobe or with lesions having a pedunculated attachment. Notable exceptions are the cases reported in 1923 by Turner[6] and by Wright.[7] The majority of successful resections of primary tumors of the liver of a sessile nature involving the right lobe have been reported within the last five years.[3, 4, 5] The present case demonstrates the feasibility of removal of a large sessile adenoma which lay just above the liver hilum and extended deeply into both right and left

lobes. This patient had undergone two previous laparotomies but no attack on the huge tumor had been essayed. Since our biopsy showed the lesion to be a benign adenoma of the hepatic cell type, we attempted resection and were able to remove the encapsulated tumor completely. The result has been quite satisfactory.

In Warvi's[8] collected series there was a recurrence rate of 21 per cent although these tumors had been classified histologically as benign adenomas. This evidence supports the view that malignant hepatomas and malignant cholangiomas not infrequently have their origins in pre-existing adenomas.[3, 4, 9] Accordingly, radical resection of these lesions is definitely indicated.

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PSEUDOCELLULITIS, A REACTION TO PENICILLIN IN PEANUT OIL AND BEESWAX

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THE ease and convenience of administering penicillin in a menstruum of peanut oil and beeswax by daily intramuscular injection, as well as its proved efficacy in the treatment of infection caused by penicillin-sensitive organisms, have prompted its wide use for a variety of infections.

This report was stimulated by the observation of four instances of severe delayed local reactions to this drug. The reactions appeared seven to ten days after the first injection. They were characterized by the rapid appearance of tense painful swelling of the entire buttock associated with severe tenderness, generalized malaise, and a temperature up to 102°. In addition there was an erysipeloid skin eruption circular in shape, the center of the circle corresponding with the site of the needle puncture of the original injection. The central zone of this eruption was somewhat cyanotic and the edge of the eruption sharp and raised. When injections had been given in both buttocks the lesion began in one and was followed within twelve to thirty-six hours by a similar but less marked reaction in the opposite buttock.

In every instance the lesion reached its peak in forty-eight hours and then receded spontaneously in seven to ten days, leaving merely a small residual tender nodule in the subcutaneous tissues along the track of the original needle puncture. This nodule then slowly receded in a further fifteen to forty-five days.

In every instance constitutional symptoms occurred, consisting of malaise and fever. In two there were also joint pains, urticaria, and rhinitis.

The initial appearance of these lesions is most suggestive of severe cellulitis of the entire buttock, complicated by erysipelas spreading from the site of the injection. However, the delay in the development of the lesion, the rapid supervention of an identical lesion in the other buttock when injections have been given bilaterally, the subsidence of the reaction without specific treatment, and the absence of either suppuration or necrosis of tissue discounts this possibility. The delay in the reaction, its rarity and lack of necrosis also exclude the possibility of simple local irritation.

One must conclude that these are allergic reactions. In addition to the fact that infection and primary irritations are excluded for the reasons already given, positive evidence for this point of view includes the following: (1) the known role of penicillin as an allergen, (2) the appearance of the reactions only after a latent period of seven to ten days in each case, (3) the association of other known manifestations of serum sickness, such as urticaria and joint pains, with the local reaction in two of the patients.

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Though skin tests were inconclusive, failure to elicit positive skin reactions does not argue against the probability of an allergic reaction, as negative skin tests are common in other drug allergies. Thus, in a series of twenty-five patients with the induced urticarial reaction to penicillin, only ten gave a positive delayed skin test to penicillin.[1] Immediate tests were negative throughout.

CASE REPORTS

CASE 1.—A 20-year-old white woman had a paronychia of the left middle finger of ten days' duration and a similar lesion of the right fifth finger of five days' duration. The local lesions were drained by pushing back the paronychium and 300,000 units of penicillin in oil and wax were given into each buttock on two successive days. The local lesions subsided in five days.

Eight days after receiving the first injection of penicillin the patient noted tender tense swelling of the right buttock. Temperature was 101° F. A similar but less severe swelling of the left buttock appeared the next day. At the same time drainage recurred from the paronychia of the left middle finger. This cleared after incision. Examination revealed a typical lesion, as just described. The lesion of the right buttock was about seven inches in diameter and that on the left about five inches in diameter. These lesions subsided spontaneously in ten days leaving indurated nodules about 1 cm. in diameter at the site of the needle puncture in both buttocks. These nodules resorbed completely in four weeks.

The patient gave no personal allergic history. Her mother had angioneurotic edema for many years. The patient's only previous and uneventful contact with penicillin had been as an ointment applied for one week some months before the present reactions. Her father and sister had pollinosis.

Skin testing with crystalline penicillin, 20,000 units per cubic centimeter, gave negative immediate and delayed reactions. Trichophytin tests with ragweed and peanut protein were negative. No other tests were done.

CASE 2.—A 45-year-old white woman had an infected sebaceous cyst in the left submaxillary region of one week's duration. She was given three daily injections, each of 300,000 units penicillin in peanut oil and beeswax. The signs of inflammation about the cyst subsided promptly. Eight days after the first injection of penicillin she noted temperature of 102° F. and tenderness of both buttocks. On the next day, both buttocks were markedly swollen and tender, and gave a sensation of deep fluctuation. In addition, there was a circular area of redness and edema of the skin with a sharp raised edge quite typical of erysipelas. The central area of the skin lesion was faintly cyanotic. Under expectant treatment the fever subsided in three days. Concomitantly the lesions in both buttocks regressed, leaving residual areas of induration along the track of the original needle punctures. The latter resorbed in five weeks, leaving both buttocks normal.

The only previous contact with penicillin was a brief course of oral penicillin one year before, to which there had been no unusual reaction. The patient gave no personal history of allergy. One brother had both hay fever and asthma, her paternal grandfather had asthma, and her daughter had eczema at 6 months.

Skin tests with crystalline penicillin gave negative immediate and delayed reactions. Bee and peanut protein tests were negative, as were common inhalants and pollens. Trichophytin test was positive.

CASE 3.—A 16-year-old white woman complained of a tender area over the tip of the coccyx of three days' duration. Examination revealed an area of cellulitis in the cleft of the buttocks over the coccyx. There was no definite fluctuation. A diagnosis of infected pilonidal cyst was made. The patient was given 300,000 units of penicillin in peanut oil and beeswax in the left buttock. By the following day, cellulitis had subsided and there was definite fluctuation. The pilonidal abscess was incised and drained. Nine days after receiving the injection of penicillin the patient complained of pain in the left buttock. Examina-

tion revealed moderate tenderness and swelling in the buttock in the region of the original needle puncture. Temperature was 100° F. The next day the temperature was 102° F., buttock was markedly swollen and edematous, tenderness was so great as to prevent ambulation. The skin over the buttocks showed an erysipeloid reaction precisely circular in shape with sharp raised border. In addition there were joint pains, urticaria, and coryza. The fever persisted for three days. The tenderness and swelling of the buttocks subsided in two weeks, leaving residual nodular infiltrations along the needle track. These subsided in a further three weeks. There was a past history of mild upper respiratory symptoms during the spring grass season for the last three years. Unfortunately the patient was not available for skin tests.

CASE 4.—A 35-year-old white woman had acute left axillary adenitis of four days' duration. Glands were hard and tender but were not fluctuant. She was given two injections of penicillin in saline solution at three-hour intervals followed by two daily injections of 300,000 units of penicillin in peanut oil and wax. The adenitis subsided in two days. Five days after the last injection of pencillin in oil and wax the patient noted small painful nodules at the sites of the injections. These lesions developed so that by the eighth day the skin over the buttocks displayed an erysipeloid lesion with sharp raised edge and cyanotic center. The buttocks had become intensely swollen and tender. The temperature was 103° F. The next day the fever subsided somewhat but the patient later developed joint pains, coryza, urticaria, and moderately severe headache. The peak of this general reaction occurred while the severe local reaction was beginning to subside. From this time on, the symptoms slowly remitted, so that eighteen days after the initial injections she was well except for small persistent nodules at the site of the injections. The latter subsided at the end of one month. In addition to symptomatic treatment she received frequent doses of ephedrine but the latter had no obvious effect on the lesion in the buttocks. One month previously the patient had had three intramuscular injections of aqueous penicillin without reaction. Some years previously the patient had developed a generalized eruption several days after treatment with sulfadiazine. She had a tendency to mild erythema and urticaria after taking warm baths and several years before had generalized urticaria for several hours. Some years previously she had had marked local swelling as a result of a bee sting.

Skin tests with crystalline penicillin gave negative immediate and delayed reactions. Tests with trichophytin were negative, with bee protein 0.001 mg. nitrogen 2 plus, with peanut extract negative. There were also positive reactions to ragweed, plantain, pyrethrum, and silk.

DISCUSSION

The reactions described in this paper are probably common. Thus the four instances here reported have occured in a series of fifty in which penicillin in peanut oil and beeswax had been administered. Other physicians have told us informally of frequent similar experiences. Despite this, only one instance of this kind appears to have been reported in the literature thus far.[2] Although indurative reactions following penicillin in peanut oil and beeswax have been mentioned by other writers, little attention appears to have been paid to these very intense delayed local responses. For example, in a large series of patients treated with this preparation of penicillin, Romansky[3] although noting local reactions does not give any description of the lesion, nor does he indicate that their appearance may be alarming.

The reaction we describe seems to be characteristic of the penicillin, oil, and beeswax preparation and not of penicillin in saline solution. In a group of well over 1,000 patients receiving multiple intramuscular injections of penicillin in saline solution we have never seen a local reaction of this kind.

It is of practical clinical importance that the general physician and surgeon be aware of this type of localized allergic reaction to penicillin in oil and beeswax, because it can be readily confused with an inflammatory lesion caused by infection. We have been informed of actual cases in which fruitless attempts at incision and drainage were made, resulting only in prolonged illness. In another patient whom we encountered, the attending physician had prescribed additional penicillin in an effort to combat the supposed local infection. The significance of this reaction as an allergic manifestation and its completely benign prognosis thus deserve wider recognition.

The probable mechanism deserves some comment. It appears likely that these severe reactions are analogous to local serum sickness. The predominant response is a local one presumably because the slowly absorbed preparation retains antigen at the site for a prolonged period for local reaction. The absence of similar reactions to penicillin injected in saline solution indicates the importance of the menstruum in determining the character of the reaction. The more general symptoms indicative of the serum sickness-like response were present in two of the cases, and fever occurred in all. It is probable that, in addition to its localizing action, the oil and wax increase the antigenicity of the penicillin, acting as an immunologic adjuvant as has been described especially by Freund and co-workers.[4]

The exact antigen causing the allergic response to penicillin in peanut oil and beeswax is not identified by the present observations. Probably it is the penicillin itself. Thus, Gay[5] reported on the lack of antigenicity of beeswax. He referred also to previous observers who gave multiple intramuscular injections of 5 per cent beeswax in peanut oil in repeated series without any subsequent local reactions being observed. Experience indicates that peanut oil itself rarely causes difficulty as is testified by the lack of reaction to epinephrine in peanut oil, even when used in atopic individuals. In Case 3 we obtained a 2 plus reaction to bee protein; this patient gave a history of intense local reaction to a bee sting some years before. However, the prolonged incubation period in this, as in the other cases, suggests a newly induced sensitivity. If the buttock inflammation were due to pre-existing sensitivity one would have anticipated its rapid development within a period of twenty-four to forty-eight hours rather than after an interval of one or more weeks.

It apppears plain that neither the beeswax itself nor the peanut oil is the probable cause of these reactions. In contrast, penicillin, whether amorphous or crystalline, has been found to induce syndromes which resemble serum sickness and other forms of allergic reaction fairly readily. In most of the instances reported, the actual antigen in the penicillin preparation has been the penicillin itself, although occasionally an impurity of some kind is the offender. This may account for the experience of Lederman,[2] who found that in his case the reaction to penicillin in peanut oil and beeswax could be avoided by changing to another brand.

In our brief series one of the patients was definitely an atopic individual; two others had a strong family history of atopic illness. Although such a con-

stitutional predisposition is doubtless not necessary to the development of this type of acquired sensitivity, it is possible that atopic persons react more readily.

The clinical management of this form of reaction to penicillin in oil and beeswax merits a little more detailed discussion. In order to reduce the occurrence of such reactions it is wise to employ a preparation containing crystalline rather than amorphous penicillin whenever possible. If a brand containing amorphous penicillin has been used it may be possible to substitute another brand, preferably of crystalline penicillin, in the hope that the actual antigen may be avoided. However, if the reaction has been a severe one and the need for further penicillin is not especially urgent it is probably best to stop penicillin therapy altogether. When the indication is urgent it is preferable to change to intramuscular crystalline penicillin in saline solution or to any of the preparations of procaine penicillin. This should be given in small doses at first and preferably injected into the deltoids. At the same time the patient can be given antihistamine drugs, epinephrine, or ephedrine as symptomatic medication. Thus it may be possible to tide the patient over this difficult period, increasing the penicillin dosage as it appears to be tolerated until full therapeutic levels are obtained. It would be advisable to observe the patient carefully for evidence of more severe allergic reactions such as intense urticaria, generalized edema or erythema, or any indication of vasomotor collapse. Should any of these occur it would then be imperative to stop the drug at once.

In most instances of newly induced penicillin sensitivity the allergic state is transient and penicillin can be re-administered without difficulty, sometimes after an interval of only a few weeks. However, this is not always the case and it therefore follows that caution must be observed in re-administering penicillin to a patient who has a history of a severe local reaction to penicillin in oil and wax such as is described in this paper.

Though in three cases in this group in which penicillin skin tests were performed, they were negative both on immediate reading and at the forty-eight hour observation, previous experience with other forms of induced penicillin allergy would suggest that in a larger series a small percentage would show a positive forty-eight hour test. This would be of value both diagnostically and as a guide to the persistence of sensitivity to penicillin. The presence of such a positive test would indicate the need for even greater caution in administering the drug. Desensitization with penicillin could be tried as it has been found effective in other forms[1, 6] of penicillin allergy.

SUMMARY

1. Four cases of a severe delayed local reaction to penicillin in oil and beeswax are presented.

2. The reaction is of such intensity as to mimic bacterial infection with cellulitis and erysipelas. Fever and malaise are usual accompaniments.

3. Although alarming in its initial appearance, the reaction resolves completely without specific treatment.

4. The allergic nature of the reaction is indicated by the latent period of seven to ten days, and by associated symptoms of urticaria and joint pains.

5. The results of skin tests with penicillin, peanut oil, and bee protein are discussed. Penicillin is considered the most probable antigenic factor, the menstruum enhancing its antigenic activity.

6. Practical clinical management is presented.

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ADVANCES IN ANESTHESIA

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ADVANCES in anesthesia follow several lines of endeavor. I shall try briefly to mention some of them. For example, the most notable situation in history exists today in the fact of the great latitude in choice of agents and methods. In nitrous oxide one has a mild, quick-acting analgesic agent associated with a short period of recovery and relative safety in respect to fire and explosion hazards. This agent is generally available, and is used rather skillfully by a large number of individuals. Ethylene similarly is generally available, and although the fire and explosion hazard which attends it has limited its use, it is still one of the outstanding agents from the standpoint of safety in the anesthetization of patients suffering from shock or heart disease. Cyclopropane is potent and is accorded widespread use. It is not free of hazard from fire and explosion, but it is capable of producing better relaxation than are any of the other gases. The period of induction is short. The occasional difficulty encountered when an untoward result is observed just as the anesthesia has been terminated is not fully understood, but apparently it is peculiar to certain techniques of the administration of cyclopropane. I refer to the so-called cyclopropane shock that is seen at the termination of anesthesia in an occasional case.

The devices with which the gases are administered have not been improved for many years, and probably will not be until adequate mechanisms for the analysis of the atmospheres within the breathing bag and various parts of the machine are developed. I think that it is safe to say that this advance can be anticipated either this year or next year.

Of the several types of ether that have been developed, none seems to be better than diethyl ether. In this centenary year of the use of chloroform it is interesting to notice that anesthesia produced with this agent still is fraught with danger, and yet chloroform has certain qualities which make it an agent tempting to many, and reports on its use from time to time are still given. It would seem that the favor originally accorded chloroform might have been more prolonged had it not been for the introduction of so many good agents in the last few years. Another agent is ethyl chloride. Very few reports concerning this agent are seen now, probably because, like chloroform, it is not generally used.

In the field of local anesthesia various agents have been introduced such as Nupercaine, Pontocaine, and others. These agents seemed to be required because prolonged anesthesia could not be maintained with a single dose of procaine hydrochloride. This was especially true in block and spinal anesthesia. Lemmon's introduction of continuous spinal anesthesia was followed by Tuohy's modification of Lemmon's method which was in general an adaptation of Adams'

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technique for the production of continuous caudal anesthesia. That is, by use of a catheter instead of a needle, it became possible to produce anesthesia of desired length with procaine hydrochloride. This was important because I believe procaine hydrochloride is the safest available agent for local anesthesia. Here is an instance in which improvement in technique has greatly increased the efficiency of an old agent, and it is an outstanding advance in anesthesia whenever that result can be obtained.

The introduction of the Magill intratracheal tube was without doubt a great advance in inhalation anesthesia. This technique is used extensively to great advantage now in many types of surgery. For intracranial operations it has made the patient's breathing quiet and has obviated the increased intracranial pressure which often occurred when an anesthetic agent such as ether was administered for this sort of operation. Use of the intratracheal tube in plastic surgery is essential so that the surgeon may have the operative field to himself and so that it may be kept sterile. One of the most important applications of the intratracheal tube is in thoracic surgery, where it permits the lungs to be inflated at will during the operation, with the thorax opened. In abdominal surgery the quietness of respiration which the technique ensures is desirable, and the ease with which the anesthetic agent can be introduced into the lungs and from there into the blood stream and thence to the nervous system has increased the efficacy of inhalation anesthesia generally. The Magill technique is especially valuable when an operation is to be performed on a patient's back and he must be placed in the prone position. In all the operations mentioned, and with all the various anesthetic agents suited to the technique, it is possible, with the tube in place, to aspirate material from the trachea and bronchial tree both during anesthesia and for a short period afterward. This decreases morbidity and mortality rates considerably.

Intravenous anesthesia gradually has won widespread favor largely because of Pentothal sodium. It is generally recognized that administration of this agent should be preceded by preliminary medication, usually with a barbiturate and morphine and atropine. The dose of Pentothal sodium should be kept relatively small; that is, usually it should not be more than 1 or 2 Gm. for a patient. It is definitely understood that solutions for Pentothal sodium stronger than 2.5 per cent are hazardous. In combining nitrous oxide and oxygen (50 per cent of each) and using this mixture in association with Pentothal sodium, we are able definitely to reduce the amount of Pentothal sodium that otherwise would be administered. The administration of small quantities of Pentothal sodium to induce anesthesia before inhalation anesthesia is begun has been much appreciated by patients. The technical point of importance in this connection is that not more than 10 c.c. of a 2.5 per cent solution of Pentothal sodium should be administered before inhalation anesthesia is begun, and it is better if the amount can be kept to 6 or 7 c.c. Larger amounts of Pentothal sodium interfere with the depth of respiration, and therefore interfere with production of the desired result with the inhalation anesthetic agent. A second technical point in the use of Pentothal sodium is that if the effect of the preliminary medication on the patient is minimal and if, when 10 or 15 c.c. of a 2.5 per cent solution of Pento-

thal sodium has been administered within a few minutes without the production of satisfactory anesthesia, then an additional dose of morphine should be injected intravenously. This additional dose usually should be ⅛ to ⅙ gr. (0.008 to 0.01 Gm.).

Nevertheless, it is realized that Pentothal sodium does not provide everything that might be desired in an intravenous anesthetic agent. Therefore, further investigations have been made for new agents, or suggestions have been advanced that something might be combined with Pentothal sodium to give it the potency which it lacks.

The question of relaxation of the patient is of prime importance to both surgeon and anesthesiologist. The advent, then, of curare in medical practice, especially in connection with the administration of anesthetic agents, has made a great impression on those who have used it. Curare produces excellent relaxation, with relatively little postoperative prostration. It has been used most commonly in association with cyclopropane anesthesia, in which relatively large quantities of oxygen are used. Curare and cyclopropane, especially when an intratracheal tube is used to administer the anesthetic agent, give a result that is highly desirable in most instances. The great impression caused by this particular combination stimulated the use of curare with nitrous oxide, ethylene, and also other anesthetic agents. In the latter instance less curare is required than when curare is used with the gases. The use of curare with Pentothal sodium has been tried repeatedly; in such a combination curare does give a degree of relaxation that Pentothal sodium in itself cannot provide. Recently, Baird suggested the use of Pentothal sodium plus curare, the curare preferably having the form of a solution of d-tubocurarine chloride. Baird was greatly impressed with the results of administration of these agents in combination in one syringe, the mixture being 0.5 mg. of d-tubocurarine chloride per cubic centimeter of 2.5 per cent solution of Pentothal sodium. At the same time, oxygen or nitrous oxide and oxygen is administered to keep the patient oxygenated.

In this respect, we ought not to forget that the anesthesiologist's understanding and actual use of stimulants and supportive measures are hardly less important than the method of anesthesia employed, whatever it may be. This is a consideration of the utmost significance which serves to emphasize the need for extension of the period of the anesthesiologist's training, to which I shall advert later.

As we look back and examine the present and speculate as to the future, it would appear that the status of anesthesia now is relatively good and that apparently it will improve. This opinion is based strictly on the agents available now and on those which it is possible to envisage. An additional important phase, however, of the present status of anesthesia is that more and more physicians have interested themselves in the field of anesthesiology. A number of institutions have established either temporary or fully approved residencies in this specialty, and in some instances prominent anesthesiologists may teach by the preceptor method. There are a national society of anesthetists, a certifying board for proficiency in the specialty, and a section of the American Medical Association, all actively devoted to the advancement of this field. The demand

for skilled physician anesthesiologists exceeds the supply, and no doubt will continue to do so for some time, but the opportunities for training have been expanding so rapidly and are being so carefully scrutinized from time to time that I cannot say that the outlook as to supply is at all hopeless. As a matter of fact, the opportunities for physicians in this field are great and will continue to become greater. The inclination now is for a physician anesthesiologist to meet only the minimal requirements of two years of training, but eventually I think such training will entail three years.

World War II substantiated the prophecy that anesthesia would become much more important after the war than it was before. It seems conservative to say that anesthesia has gained great momentum and an important position in the United States, Canada, and the British Isles, and that it is also gaining considerable momentum in most other modern countries throughout the world. As I have said, the present status of anesthesia may be considered to be excellent, in so far as the beginning of the second centenary of its use is concerned, especially when we realize that much of the progress was made in the first few years and the last few years of the first centenary of its use.

THE APPLICATION OF MYOTOMY TO TENDON REPAIR IN THE FINGERS

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SEVERAL years ago myotomy was introduced as a maneuver facilitating the repair of divided flexor tendons of the hand.[1] With growing experience it soon became apparent that this procedure possessed several virtues.[2] It not only makes easier the handling of the divided tendon ends by eliminating the usual tension but obviates the danger of disruption of the suture line, as well. Finer suture material can be used and early active motion is permissible.

This presentation is particularly concerned with the application of myotomy to tendon lacerations in the proximal and middle phalanges of the fingers. This is the area where the worst results are to be expected. Bunnell[3] has discussed the reasons for this and has described his method of handling the problem. With the aid of myotomy, it is possible to treat the situation somewhat differently to attain the objective.

The incision advised by Bunnell is used. It runs from the web to just beyond the distal flexion crease on the lateral surface of the finger midway between the volar and dorsal aspects. The dissection plane is directed posterior to the volar digital nerve and vessels, and exposes the entire extent of the digital flexor sheath, regardless of the location of the wound. The proximal tendon end is sought for and seized with an artery forceps. Every effort is naturally made to disturb the sheath as little as possible. A linear incision is then made just above the wrist and the corresponding muscle belly identified as shown in Fig. 1. Where the sublimis tendon is also cut, it is excised, only the profundus being repaired. As much of the distal portion of sublimis tendon is cut away as can easily be delivered into the wound.

Following the myotomy, the proximal profundus tendon end is then pulled down toward the point of tendon insertion at the base of the distal phalanx. If the degree of release allows it to reach all the way, the entire distal tendon end is resected and the proximal end is then sutured as shown in Fig. 2 to the base of the distal phalanx and the attached stump of tendon insertion. Where it is not possible to bring the proximal end this far, less of the distal tendon is resected so that the suture site lies somewhere in the middle phalanx at a point distal to the location of the wound. A cuff of sheath is preserved on the middle phalanx through which the tendon is passed.

The finger can be splinted postoperatively in extension with slight flexion at the wrist. The advantage of avoiding a bulky tendon suture at the site of injury of the sheath, surrounding tissues, and skin is obvious.

The indications for immediate tendon repair have remained the same in principle on this Hand Service as at the time of their original adoption in 1933 following the publication of the article of Koch and Mason.[4] In two of the

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three illustrative cases presented in detail the requirements for immediate tenorrhaphy were satisfied. It may be parenthetically added that the advent of penicillin has not altered our insistence on a reasonably clean wound in addition to other factors before proceeding with operative treatment in the fresh case.

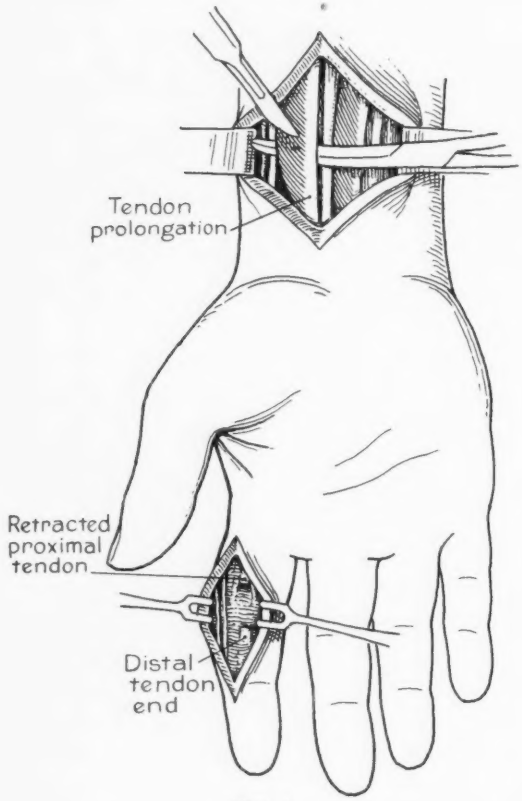

Fig. 1.

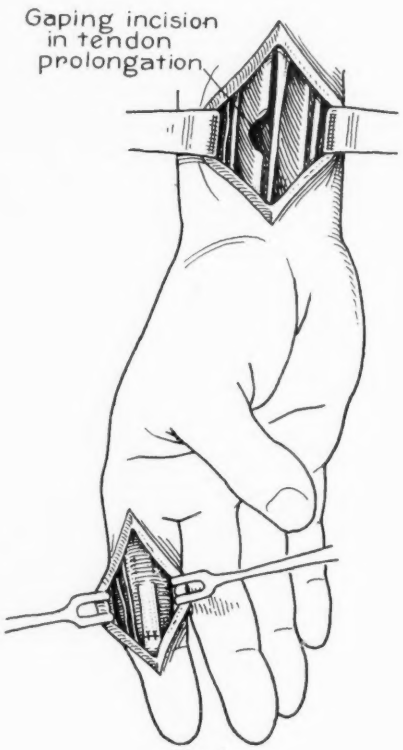

Fig. 2.

Fig. 1.—In this illustration the site of tendon division has been exposed, the proximal tendon end has been identified, and the corresponding profundus muscle belly has been delivered into the wrist wound.

Fig. 2.—Myotomy, which consists of division of the tendon prolongation leaving 3 or 4 cm. of muscle functioning below the point of division, has been performed. The proximal end as a result of this release of tension has been pulled down to the site of tendon insertion where it is sutured into place. The excess distal tendon has been excised.

CASE REPORTS

T. R. (Admission 47637), a 50-year-old housewife, was admitted Sept. 8, 1946, shortly after cutting the right ring and little fingers while preparing lunch. She suffered two sliced lacerations of the volar aspects of both fingers at the proximal interphalangeal joints. Examination revealed evidence of division of both flexor tendons to the little finger as well as of the volar ulnar digital nerve to the finger. In the ring finger the flexor profundus tendon had been divided. Under general anesthesia and with the aid of an Esmarch bandage, profundus tenorrhaphy and neurorrhaphy were performed. Myotomy was successfully used. In both fingers the distal tendon ends were excised down toward their insertion so that the tenorrhaphy site was located near the insertion in the terminal phalanx well away from the wounds in the sheath and integuments. A posterior moulded plaster splint was then applied and left on for twenty-five days. This patient improved progressively but when last seen several months after operation still showed some defect in complete flexion in both fingers.

G. O'D. (Admission 48410), a 31-year-old fireman, was admitted on Jan. 27, 1947, shortly after cutting the middle phalanx of the left middle finger on broken glass. He suffered a division of the flexor profundus tendon and of the volar digital nerve on the radial side. Following the usual technique a myotomy was performed which allowed the suture of the proximal tendon end into the normal insertion site of the tendon at the base of the terminal phalanx. Neurorrhaphy was simultaneously performed. This patient was able to flex his finger completely within four months. Sensation was normal.

S. M. (Admission 48839), a 24-year-old clerk, had originally suffered a laceration on the volar aspect of the middle phalanx of the right index finger on Feb. 3, 1947. The wound was dirty, for which reason only the skin was sutured and an infection ultimately developed with pus formation. By April 25, 1947, repair of the divided flexor profundus tendon which had been recognized as being present after injury was deemed safe. Following the usual technique the profundus tendon end was found and dissected free from somewhat dense adhesions. Following myotomy it was possible to perform tenorrhaphy near the tendon insertion. The usual plaster immobilization for twenty-five days was then followed, after which time physiotherapy was begun. This patient regained complete function of the finger within four months.

SUMMARY

Three cases in which myotomy has been performed to facilitate the repair of flexor tendons divided in the fingers are presented.

The procedure of myotomy is a simple technical expedient that makes possible the easier handling of these cases and allows the attainment of certain desirable objectives in this type of surgery.

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MULTIPLE PRIMARY CARCINOMA

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SINCE 1869, when Billroth[1] reported the first two cases of multiple primary malignancy, a gradually increasing interest in the subject has been aroused. Through the succeeding years much data have accumulated on the subject until at this time the condition, which was once considered a rare phenomenon, is recognized as being fairly common and the reporting of sporadic cases is hardly justified unless the material will be a definite contribution.

In view of the manifold and bizarre nature of malignant growths, it was immediately necessary to set up criteria, the fulfillment of which were intended to establish the independency of the various lesions, and the following were Billroth's postulates: (1) Each tumor must have an independent histologic appearance; (2) the tumors must arise in different locations; and (3) each tumor must produce its own metastases. A few years later, Mercanton[2] advocated the addition of a fourth postulate: That the patient remain free from the disease following operation, thereby demonstrating that the growths were separate entities and were not themselves metastases. In light of present knowledge of cancer it is obvious that, in the interests of critical evaluation, these criteria cannot be rigidly adhered to. As Seecof[7] has pointed out, metastases and recurrences frequently show marked cell change from original cell type. Conversely, multiple malignant growths occurring in systems or paired organs may readily be primary growths although exhibiting like histologic pictures. Because of change in cell type during metastasis it may be possible to confuse such growth, concluding it to be the primary focus and again, because of these changes in cell type, it may not be possible to prove that an apparently primary growth is not a metastasis. These facts, together with the knowledge that malignant tumors may exist without metastases, are evidences of the weaknesses in these postulates. Kretschmer[36] also referred to the difficulty in meeting the third postulate in that the patient may, and preferably does, come early in the course of the disease, long before metastases have had time to develop. He also points out that metastases may be so small as not to be demonstrable clinically. Goetze[4] advocated a revision of these criteria as follows: (1) The tumors must have the macroscopic and microscopic appearance of the usual tumors of the organs involved; (2) exclusion of the probability of one tumor being the metastasis must be certain; and (3) the diagnosis may be confirmed by the character of the individual metastases. While the authors of several excellent papers, notably Hanlon,[9] Hurt and Broders,[12] and Stalker and associates,[27] have followed these postulates, there remains the possibility of error due to the fact that in the diagnosis of multiple malignancy, the exclusion of the possibility of one neoplasm being a metastasis may pose a most difficult problem. Realizing this, Warren and Gates[11] have set up the following criteria which have now gained general acceptance: (1) Each of the tumors must present a definite picture of malignancy; (2) each must be distinct; and (3) the probability of one being the metastasis of the other must be excluded. That this does not completely

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satisfy all requirements is borne out by the almost universal suspicion of multiple neoplasms of certain systems, such as skin, of paired organs such as breast and ovaries, as well as stomach and colon. Also in question are some of the more complex type of growths such as carcinosarcoma, lymphosarcoma, multiple myelomas, and similar lesions noted for multiplicity. In the more critical surveys many of such types of cases have been excluded.

The incidence of multiple malignant neoplasms has been variously reported from 0.9 per cent to 7.8 per cent of all malignant cases. Hanlon[9] reported 18 cases of multiple primary malignancy in 950 cases of malignant tumors, or 2.5 per cent. Warren and Gates,[11] in 1932, were the first to make a critical survey of the literature. They reported 40 cases in 1,078 cancer autopsies, or 3.7 per cent, and in addition, analyzed 1,219 cases of multiple primary malignancy collected from the literature. For the entire 1,259 cases the incidence was found to be 1.8 per cent when American and European data were combined and 3.9 per cent for American data alone. Hurt and Broders[12] reported 71 cases of multiple primary malignancy in 2,124 cancer cases, or 3.3 per cent. Lund[13] found 94 multiple cases in 1,548 cases of cancer of the mouth, 31 of which were multiple cancer of the buccal mucosa alone, or 6 per cent. Bugher[16] found 30 cases in 983 cancer autopsies, or 3.1 per cent. In this same paper, after working out an elaborate statistical analysis, he concluded that the actual incidence of multiple primary malignancy exceeds the expected incidence on the basis of chance alone and that there is an inherent susceptibility to cancer, possessed by a portion of the population. This idea is supported by most authors. Schreiner and Wehr[15] found 307 multiple cases in 11,212 cancer cases, or 2.7 per cent. Burke[18] reported an incidence of 7.8 per cent with 46 multiple cases in 583 cancer autopsies. Austin[24] reported 887 cancer autopsies with 2.7 per cent of multiple cancers. Kirshbaum and Shively[25] found 1.2 per cent in 1,411 cancer autopsies and Desaive[26] reported 3,115 cancer cases, eliminating all cases of multiple tumors of the same system, finding 36 cases of multiple growths, or 1.2 per cent. He also cited Regaud as reporting the lowest incidence, 0.9 per cent, with only 9 multiple malignancies in 1,099 surgical cases of cancer. Stalker and co-workers[27] reported 113 cases of multiple growths in 2,500 surgical cases of cancer, or 4.5 per cent. Gaudin[29] reported 5.5 per cent of multiple growths in 4,610 cancer patients on whom follow-up studies were carried out for 40 years. Peller[30] found 270 multiple cases, 4.6 per cent, in 5,876 cancer cases and believed that the actual rate for multiple malignant growths was less than the expected rate. Phillips[32] reported multiple skin cancers may vary from 2.0 to 23.0 per cent per patient, with an average incidence of 16.0 per cent. This substantiates the findings of almost all authors that the highest incidence of multiple malignant growths occurs in the skin. It is also of interest in this respect, that Gaudin[29] has pointed out that 20.0 per cent of all patients with skin cancers had more than one primary malignant growth. Tullis[33] found 2.0 per cent of multiple malignancies in 1,044 cancer autopsies. Hellendall[34] found 4.3 per cent in 658 cancer autopsies.

Of all publications on this subject, the recent work of Warren and Ehrenreich[35] represents the most extensive and thorough investigation for it includes

the study of 194 additional cases of multiple malignancies which, combined with the data from the previous report of Warren and Gates,[11] represents a study of 1,453 cases of multiple primary malignancy. Of these cases, 234 cases represent their own material, secured from 3,907 cancer autopsies, or an incidence of 6.0 per cent. Other significant data brought out by this wide experience may be mentioned; the average age for males with multiple malignancy was 65.2 years, for females 56.9 years; sex ratio showed a preponderance of males, 2:1.1; autopsies revealed a higher incidence of multiplicity in males, whereas surgical experience gave a higher incidence in females. A study of the distribution, by site, of the lesions showed that the large intestine was involved in 35.6 per cent, prostate in 26.8 per cent, skin 17.5 per cent, pharynx 16.0 per cent, stomach 13.9 per cent, breast 12.9 per cent, uterus 11.3 per cent, with miscellaneous organs accounting for the remainder. They concluded that there is no constant ratio between organs involved in series of one cancer and in series of two or more cancers, with the exception of the large bowel. Study of the survival rates indicated that multiple malignant growths in themselves did not alter the survival rate to any appreciable degree. From their data, they believed that the presence of numerous malignant tumors did not necessarily imply a worse prognosis.

The literature contains few publications of cases presenting three or more primary malignancies in the same individual, since the condition is extremely rare. Warren and Gates[11] found only three cases. McNamara,[14] Kulikowska and Hoerner,[17] Davis and Hanelin,[19] Nemours-auguste,[20] and Portuondo[21] reported only 1 each and in 2 of these the third tumor was found only at autopsy. Warren and Ehrenreich[35] reported 1 case. Drooker[23] determined that in general, triple malignancies of miscellaneous organs comprise 2.9 per cent of all cases of multiple malignancy. Councillor and Butsch[22] stated that multiple malignant tumors of the same organ are much more rare than the incidence in different organs.

Almost equally limited in number are those cases of multiple primary malignancy in which the thyroid gland is involved. In triple malignancy, where two of the primary tumors originate in the thyroid, it is possible that only one case, other than that reported here, has appeared in the literature. Saltykow[3] reported 1 case of adenocarcinoma of the breast and carcinoma of the thyroid. Wenulet[5] was reported by Neprjachin[8] as having had a case of carcinoma of the thyroid with carcinoma of the uterus. Taschiro[6] reported 1 case of carcinoma of the prostate with osteochondrosarcoma of the thyroid. Hanlon's[9] series contained 4 cases: adenocarcinoma of the thyroid (this is listed as "adenocarcinomas" so that it is possible that in this case there were multiple primary growths in the thyroid) and scirrhous carcinoma of the breast; papillary carcinoma of the ovary and adenocarcinoma of the thyroid; adenocarcinoma of the thyroid and adenocarcinoma of the kidney; and adenocarcinoma of the thyroid with adenocarcinoma of the colon. Goriainowa and Schabad[10] reported 1 case of carcinoma of the thyroid and carcinoma of the uterus. Hurt and Broders[12] had 1 case of adenocarcinoma of the thyroid with lymphosarcoma of the groin. Schreiner and Wehr[15] had 1 case with carcinoma of the thyroid and carcinoma of the breast. Stalker[27] listed 2 cases in which the thyroid was one of the organs involved but other details were not given. Markowitz and Huerta[28] reported 1

case of adenocarcinoma of the thyroid, bilateral embryonal cell carcinoma of the ovaries, and carcinoma simplex of the breast. White[31] had one case of adenocarcinoma of the thyroid with squamous-cell epithelioma of the lip. Warren and Ehrenreich[35] reported 4 cases: 2 were adenocarcinomas and 2 were carcinoma simplex of the thyroid with the other organs involved being uterus, esophagus, breast, and prostate.

CASE HISTORY

Mrs. I. H. Only the pertinent findings are given. The chief complaint was "goiter." An enlargement in the neck had been noted first twenty-five years previously. Severe attacks of choking had occurred five years later following the deaths of mother and sister within a short interval. The enlargement then subsided for about one year, when it again slowly started to grow and continued to increase in size afterward. In the year preceding admission there was troublesome choking and strangling when drinking liquids. Nervousness started five years before and increased. She was easily excited, cried easily, became blue and depressed, and worried a great deal. In the past year she tired easily and there was increased difficulty in sleeping. Crowds of people made her nervous. In the past year she had noticed increased irritability from sources usually considered insignificant. There had been weakness of the knees on going up stairs. The patient had always slept with feet out of the covers but heat intolerance had increased in the past few months. Shortness of breath was present during past few months and was produced by moderate activities which had heretofore not bothered her. Mild exertion caused the heart to beat faster than usual. She felt tired and worn out in the mornings. Appetite had always been good but a marked increase had been noted in the past six months. There was a gain of ten pounds in the past year. She had to clear her throat frequently and was bothered by a slight hoarseness. A friend, whom she had not seen for a number of years, noted a decided change in her voice. There was no voice loss.

History of past illnesses revealed an operation in 1935 for removal of a tumor of the "womb." (This was probably a polyp.) Following this, for several months, she was bothered by a fluttering of the heart. Five years before admission she was advised to have thyroidectomy and was placed on iodine medication in preparation. She did not come to surgery and noted no improvement in the condition from the medication. For the past year she had menorrhagia with periods lasting from two to seven weeks. This was controlled by injections from her local physician.

Family history was of significance only in that there was no history of cancer or goiter.

Physical examination showed the forehead wrinkled poorly on looking up. There was visible and palpable enlargement of the isthmus of the thyroid gland which moved ordinarily on palpation and swallowing. It was firm but not hard and not sensitive to manipulation. The breasts were large and there was a movable mass in the right breast at about 12 o'clock which was about 2 inches in diameter. This mass was discrete but not encapsulated. It was not attached and was freely movable. There were no palpable nodes in the pectoral or axillary groups. The blood pressure was 170/70 and the rate 84. There was a slight tremor of the outstretched fingers. There were many skin tumors on the face and back, several of which were pigmented. The skin of the entire body showed the usual vasomotor flush with intensification on the neck and back where there was dermographia. Rectocele and cystocele of third degree were present.

Laboratory examination revealed a red blood cell count of 4,410,000, hemoglobin 70 per cent, white blood cell count of 8,800; differential, polymorphonuclears 80 per cent, lymphocytes 17 per cent, monocytes 2 per cent, eosinophiles 1 per cent; urinalysis: specific gravity 1.025, amber, acid reaction, faint trace of albumin, negative for sugar, blood or pus; basal metabolic rate, plus 4.

Operative record showed that the patient was admitted to the hospital April 3, 1945, and on the following day subtotal thyroidectomy was performed. At exploration both lobes and the isthmus were enlarged and a pyramidal lobe was present on the left side.

The right lobe was larger than the left and contained a discrete nodule (Fig. 1) measuring about 1 inch in diameter, arising from the anteromedial surface near the lower pole and overriding the isthmus. The isthmus was also found to contain a discrete nodule (Fig. 3) measuring about three-fourths of an inch in diameter, located at its juncture with the left lobe of the thyroid. Both lobes, isthmus, and pyramidal lobe were removed leaving a small stump on both sides, each of which measured about 1 inch by ½ inch. A small nodule of tissue inferior to the left lower pole was removed and proved to be thymus.

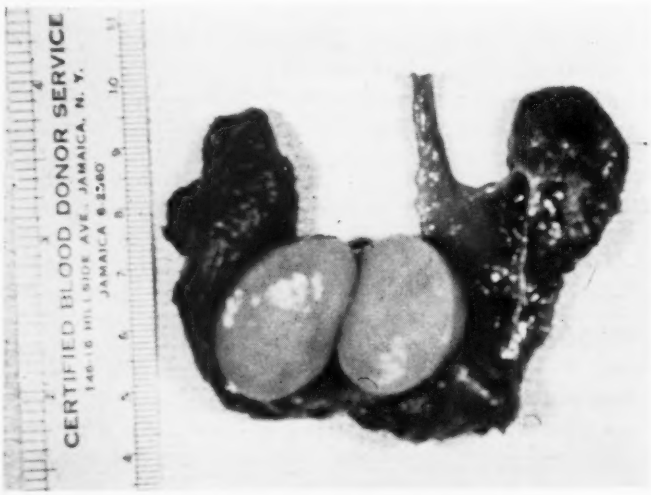

Fig. 1.—Thyroid gland with pyramidal lobe, showing section of larger tumor located in lower right lobe.

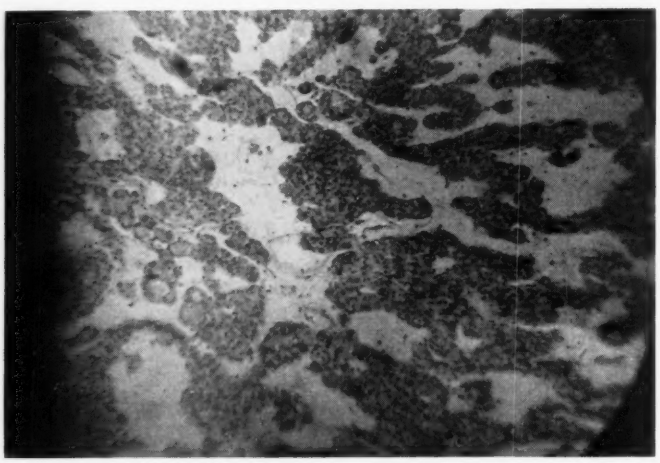

Fig. 2.—Photomicrograph of larger tumor (Fig. 1) showing cordlike arrangements of cells; early malignant change.

Pathologic report described a gross specimen consisting of both lobes of the thyroid, isthmus, and pyramidal lobe, weight 30 grams. The main thyroid tissue presented nothing unusual. In the lower right lobe there was a nodule which on section was round, pinkish white, well encapsulated, and measured 3 cm. in diameter. There was an identical nodule at the puncture of the isthmus and the lower left lobe which measured 1.5 cm. in diameter.

Microscopic examination of a section of the nodule from the right lobe (Fig. 2) showed a combination fibrous and pseudocapsule. There was no cellular infiltration of the capsule. Contents of the tumor were of rather homogeneous cell structure. There was no

definite acini formation. The cells showed a large vesiculated type of nucleus with faintly staining nucleoli. The nucleus was surrounded by a moderate amount of eosinophilic protoplasm which was finely granular. Occasional eosinophiles were seen. Only an occasional mitotic figure was observed. The general picture showed a tendency to a cordlike arrangement of the cells. There were some areas filled with hyalin-like material. In one area some small, well-formed acini were seen. Some areas showed a definite strandlike arrangement of the cellular structures with small well-formed acini in strands. Only a small amount of connective tissue stroma was present.

Section of the smaller nodule (Fig. 4) showed a dense inner fibrous capsule and outer pseudocapsule. There was no cellular infiltration of the capsule. The cellular structure of this tumor was a magnified picture of the previously described nodule. Here the nucleus

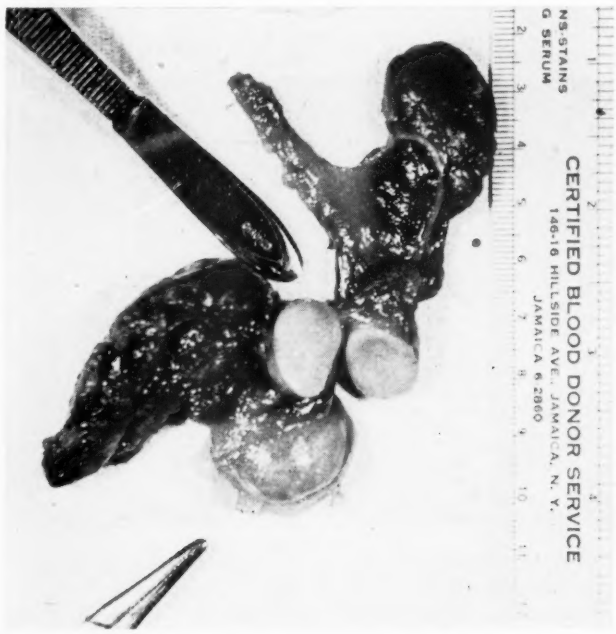

Fig. 3.—Thyroid gland showing section of smaller tumor located at juncture of isthmus with lower left lobe; hemostat points to larger tumor as seen in Fig. 1.

Fig. 4.—Photomicrograph of smaller tumor (Fig. 3); malignancy of high grade.

of the cell was markedly hyperchromatic, large, vesiculated, and showed 1 to 2 nucleoli. There was marked pleomorphism and there were many multinucleated cells. There was a moderate amount of cytoplasm which was brownish with a finely granular appearance. There was an occasional suggestion of acinus formation.

Note: These tumors appeared to be separate entities, probably both arising from separate fetal adenomas.

Diagnosis was double adenocarcinoma of the thyroid, one showing well-advanced, the other, early malignant change.

Following an uneventful recovery from thyroidectomy the patient was returned to surgery April 12, 1945, at which time radical right mastectomy was performed.

Operative record listed radical right mastectomy with dissection of axillary fat which contained a number of small soft pink lymph nodes.

Pathologic report was scirrhous carcinoma of the breast, grade 4 (Fig. 5).

Fig. 5.—Photomicrograph of breast tumor; carcinoma, grade 4.

Again following uneventful recovery the patient was dismissed from the hospital April 17, 1945. She was then given radiation therapy, receiving 1,200 r to the thyroid area and 1,400 r to each of the three breast areas. This was submitted to with some reluctance as she felt that the two operations should have been sufficient. We have been advised by the local referring physician that the patient died about six months later of generalized metastases. It is regrettable that we were unable to make additional studies on this case through the use of radioactive iodine in an effort to identify the recurrent growths. Since biopsy or autopsy was not performed at that time we are unable to state the nature of the growth responsible for the terminal illness.

SUMMARY

1. Criteria for the establishment of independent malignancy of multiple origin are outlined with discussion of limitations.

2. Incidence of multiple malignant neoplasms, as reported in the various studies in the literature, is given.

3. Other statistics, as determined by previous surveys, are reported.

4. Triple primary malignancy is extremely rare. The limited number of these previously reported are cited.

5. One case of triple primary malignancy, in which two of the primary growths originated in the thyroid, is reported here. Double primary malignancy of the thyroid gland is most unusual.

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DUPLICATION OF THE ENTIRE COLON AND LOWER ILEUM, WITH TERMINATION OF ONE COLON INTO A VAGINAL ANUS

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DUPLICATION of the entire colon appears to be a very rare anomaly. Weber and Dixon* in reporting their patient, a woman aged 27 years, reviewed the literature and were able to find only six previously recorded instances (1900 to 1945). In one of these (Gray) there was triplication of the colon. The patient, an infant, lived nine months and the situation was discovered at necropsy. Because of the rarity of this condition, the following case history is recorded and includes an account of the manner in which the anomaly was dealt with surgically.

CASE REPORT

C. A. W., female aged 7 years, was admitted Sept. 28, 1947. In 1942 she had a "swollen abdomen" and was operated upon in another institution where an "abdominal tumor" was found but not excised or biopsied. The mass appeared to be situated in the lower right abdomen, and fixed to the posterior right pelvic wall. The abdomen was closed, after exploration a clinical diagnosis of sarcoma made, and x-ray therapy administered. A vaginal anus had been noted prior to operation.

Because of the suspected abdominal tumor the patient was referred to the Memorial Hospital for further management. Upon admission physical examination was essentially negative except for constant soiling of the vulva by feces, and the presence of a vaginal anus on the posterior vaginal wall just within the vaginal orifice in addition to the normally placed anus. When probed it did not lead into a common anal colon with the normal anus, but seemed to lead to a bowel that was separated from the normal anal colon by a partition. Examination of the abdomen was otherwise negative except for a lower right rectus abdominal incision scar. There were no palpable masses. The vulva was otherwise negative. Roentgenograms also showed anomalous development of the first and second ribs on both sides with forking synchondrosis and upper thoracic asymmetry.

Later, under anesthesia a urethral catheter was passed upward through the vaginal anus and it was found that this led into a bowel which was separate from the normally placed rectal colon. Further x-ray studies were carried out with enemas of contrast media and the presence of two completely distinct colons was discovered (Figs. 1 and 2).

A laparotomy was performed with the purpose of suppressing the function of the colon above the vaginal anus in order that all stools would be passed via the normal route.

The abdomen was entered through a low midline incision. Inspection and palpation of the pelvis revealed what apparently was a normal infantile uterus, tubes, and ovaries. The pelvic and descending colons were duplicated and closely applied (Fig. 3). Blood vessels were present in the sulcus between the two bowels. The latter were thickened and devoid of haustrations and teniae; they appeared similar to what could have been hypertrophied segments of small bowel. In the region of the splenic flexure, haustrations and

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*Weber, H. M. and Dixon, Claude F.: Duplication of the Entire Large Intestine (Colon Duplex) Radiology 55: 319, 1946.

teniae muscularis appeared and extended proximally. The transverse colon appeared as a single bowel (Fig. 3) but a thin septum was visible through the walls dividing the lumen in two. In the lower ascending colon the bowel again became separated leading to two ceca with two appendices, each cecum with its own mesentery. For a distance of approximately ten inches above the ceca, there were two separate ilea, the two fusing into one proximally. No Meckel's diverticulum was present (Fig. 4, *A* and *B*).

The remainder of the abdominal viscera appeared normal.

The two appendices were excised.

Fig. 1.

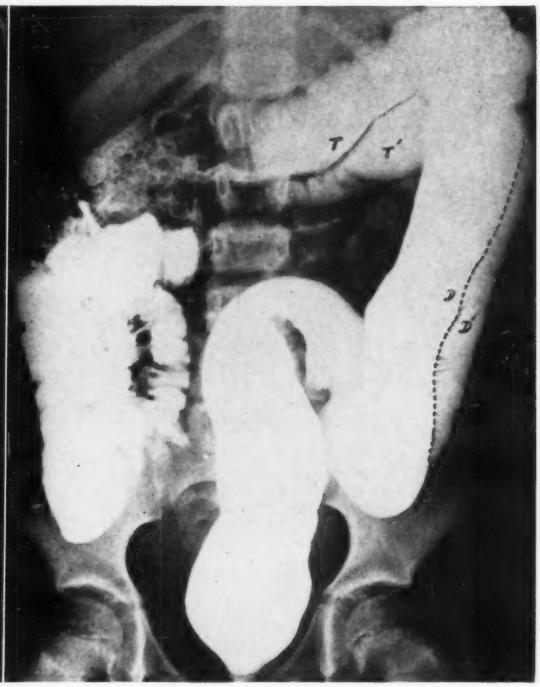


Fig. 2.

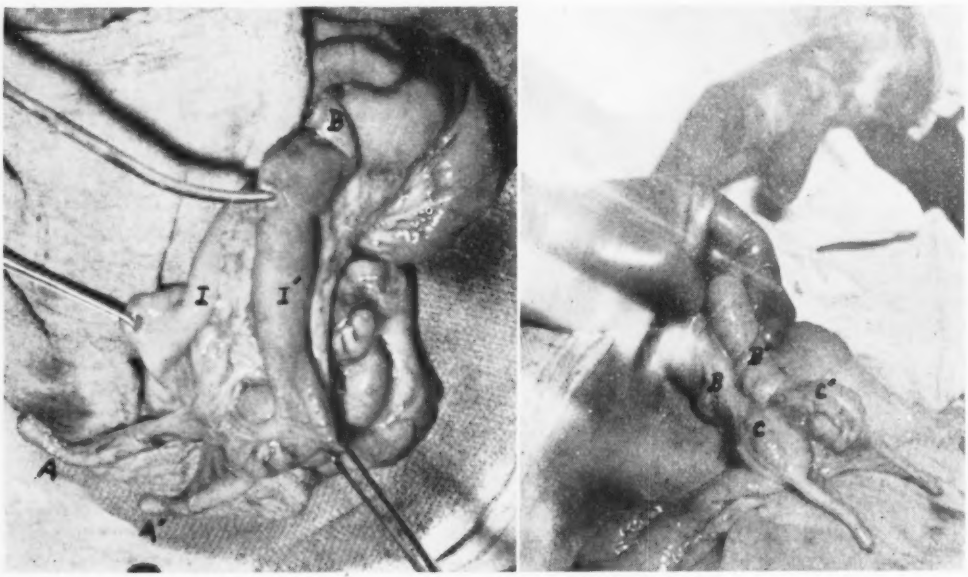
Fig. 1.—Barium enema fluoroscopy showing *P,P'*, both pelvic colons; *H,H'*, both hepatic flexures; *A,A'*, both ascending colons; and *S,S'*, both sigmoids.

Fig. 2.—Barium enema fluoroscopy showing *T,T'*, double transverse colons, and *D,D'*, both descending colons.

A rubber-covered bowel clamp was placed across the mid-descending colon, and in the upper sigmoid area parallel incisions were made, through the bowel walls into the lumens for a distance of about 4 cm. The inner margins of the wounds were sewed together with continuous catgut suture (for hemostasis) and the remainder of the anastomosis was completed with two rows of continuous catgut suture. About 2 cm. below the anastomosis the mesial one of the two colons was completely divided. The upper wound was closed by continuous catgut suture, taking all layers. The lower wound was treated in similar manner. The seromuscular layers were then approximated on each side over the previous row by similar suture and the two wounds "sealed" by interrupted sutures between seromuscularis on each side of the transection. The abdominal wound was closed in layers (Fig. 5).

Convalescence was uneventful. A normal bowel movement was passed on the sixth day. There did not appear to be appreciable mucous secretion from the lower blind segment of colon through the vagina.

Fig. 3.—Photograph taken at operation showing, *T*, transverse colons, closely applied and exhibiting haustrations and teniae mascularis; *D*, the two descending and sigmoid colons, that appear as separate structures; there are no haustrations and the muscularis appears similar to that of the small bowel.



A. *B.*

Fig. 4.—*A*, Photograph showing *A,A'*, the two appendices; and *I,I'*, the ilea which fuse into one at *B*. *B*, Photograph showing the two ceca, *C,C'*, each with its appendix, and *B,B'*, the two ascending colons.

At the operation just described no evidence of an abdominal tumor was observed. An explanation of the previous operative finding is that the inner sigmoid colon was filled and distended with fecal material. This explanation is supported by the fact that during the preoperative preparation for the last laparotomy it was very difficult to secure evacuation of this segment of the colon, which seemed to act as a reservoir for fecal material.

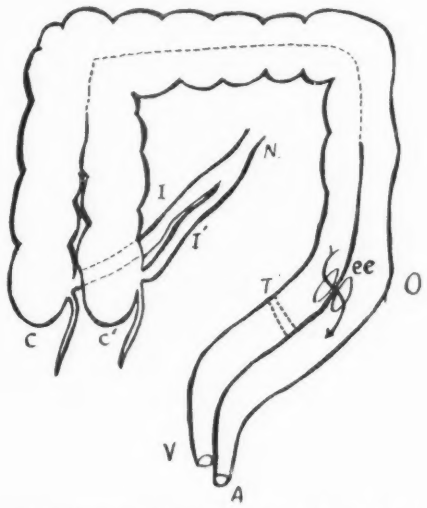


Fig. 5.—Diagram showing duplication of entire colon and lower segment of ileum as found at laparotomy in patient described in text. *N*, lower ileum divided into two separate ilea, *I,I'*. Two ceca, *c,c'*, each with an appendix. Major portions of ascending colon were separated but became closely approximated at hepatic flexure where septum separated lumina until upper portion of descending colon where two separated bowels again appeared. *O*, Region of sigmoid where operation was performed, *ee* (colo-colostomy) and *T*, transection of mesial sigmoid, to shunt all fecal material into lateral bowel which terminated at *A*, normally situated anus. *V*, Vaginal anus, at which the inner colon terminated.

It is planned in the case described to postpone obliteration of the vaginal anus until later in life when the child has grown and the parts are larger, and hence more easily handled. The lower end of the blinded segment of colon could be shunted into the lower functioning pelvic colon, or this blinded segment could be resected completely, a more extensive procedure.

In September, 1948, the patient remains well; there is only a small mucoid discharge from the vagina.

SUMMARY

The case of a female child with complete duplication of the colon including ceca, appendices, and lower ilea is presented. One of the colons terminated in a vaginal anus. The procedures in shunting all the fecal material into the normally situated colon and anus are described.

The anomaly appears to be quite rare as this is the eighth patient reported in the literature.

GASEOUS DISTENTION OF THE LATEX BAG IN THE USE OF THE SINGLE LUMEN INTESTINAL TUBE

Its Cause and Prevention

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(From the Departments of Pathology and Surgery, Mount Zion Hospital)

IN THE clinical use of the Harris single lumen intestinal tube,[1] several cases were encountered in which considerable difficulty was experienced in withdrawing the tube. The tubes were caught at either the ileocecal valve, pylorus, or just beyond the site of the partial obstruction. In these instances, after the tube was either forcefully withdrawn, allowed to pass per rectum, or removed at enterostomy, the latex bag was observed to be distended with gas. The purpose of the experiments reported here was to elucidate the mechanism of this distention with a view to formulating a satisfactory method for its prevention.

Since the bag became distended with no apparent source of gas other than by diffusion across the wall of the bag, it seemed probable that we were dealing with an osmotic phenomenon. The wall of the latex bag must then be permeable to one or more gases in the bowel and relatively impermeable to one or more gases in the air. The gas which diffused into the bag must be one which is present in low concentration in the air but in higher concentration within the bowel. Under these circumstances the permeable gas would diffuse into the bag until its partial pressure within the bag equalled its partial pressure within the bowel, or until its diffusion was prevented by the counterpressure of the distended bag. If this explanation of the bag dilatation were true, this distention could be prevented, regardless of the exact nature of the gases in the bowel lumen, by removing all traces of nondiffusible gases from the bag before its introduction into the bowel.

In order to test this explanation, 4 c.c. of mercury were placed in a latex bag. This bag was then thoroughly flushed with carbon dioxide to remove all traces of air. The bag was then compressed to expel most of the gas, leaving the bag almost empty and simulating the condition of the bag as it is used clinically. A control bag was similarly prepared without being flushed with carbon dioxide. These bags were then suspended in an atmosphere of approximately pure carbon dioxide. Within one day the control bag became distended and tense, while the bag which had been flushed with carbon dioxide remained in its initial collapsed and flaccid state. This experiment has been repeated several times, and the exposures were extended over a period of one month. The results were always identical with those of the first experiment. When the exposure was prolonged, there was never any significant change after the first day. These experiments were also performed with methane, which was found to be relatively nondiffusible across the latex wall.

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SUMMARY AND CONCLUSIONS

In the use of single lumen intestinal tubes utilizing rubber or latex bags weighted with mercury as a means of propulsion, the factors determining distention of the bag are: (1) permeability of the latex bag, (2) concentration of the diffusible gases in the bowel, and (3) the duration of the exposure within the bowel. The variations in these three factors undoubtedly account for the relative infrequency of complications due to excessive gaseous distention of the bag. However, this complication can be entirely avoided in all cases if the latex bags are flushed with carbon dioxide before they are attached to the intestinal tube.

ADDENDUM

Subsequent to the time that this paper was submitted for publication, a paper by Cantor, Phelps, and Esling on this same problem has been published.[2] In their paper they reported the results of an extensive quantitative investigation of the permeability characteristics of the various rubber balloons used on intestinal tubes. It is gratifying to note that their studies completely substantiate our observations regarding the permeability of latex. They recommended the use of a less permeable rubber bag (neoprene-G) tied firmly enough to prevent loss of the mercury yet sufficiently loose to permit gases to escape. No doubt their method is effective if their recommendations are carried out, but we believe that the procedure of removing air from the balloons by flushing with carbon dioxide just prior to sealing them will prove to be a simpler and more certain prevention of gaseous distention.

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ONLAY GAUZE PRESSURE DRESSING

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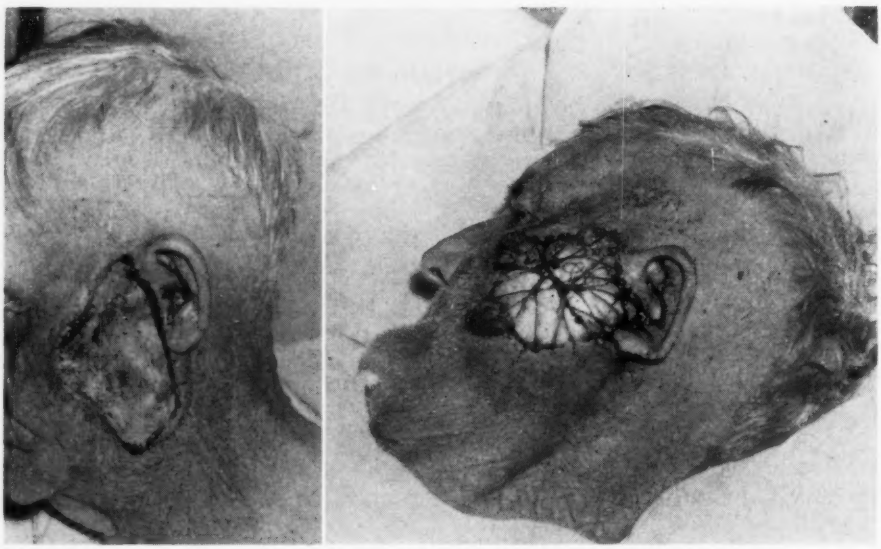
SKIN transplants are successfully held in situ by simple gauze pressure dressings tied on by peripherally placed long cotton sutures.

A skin transplant is accurately approximated to the prepared recipient area and carefully sutured margin-to-margin by interrupted No. 24 cotton sutures placed every one-quarter inch. These sutures are fourteen inches long and are tied in their midportion, leaving two equal lengths which are laid back radially from the periphery.

Gauze is fluffed, folded, or rolled into a suitable mass to cover accurately the full perimeter of the skin transplant. This gauze is then appropriately ensheathed by carefully wrapping with penicillin-benzocaine-lanolin impregnated gauze. This lanolin gauze is of moderate coarse mesh and is applied in a single and not multiple thickness.



A. *B.*

Fig. 1 (Case 1).—*A* and *B*, J. S., University Hospital, operated upon oct. 13, 1947; resection parotid tumor.

It is important that blood serum and pus may drain freely through the multiple perforations of the skin transplant and through the meshes of the grease gauze dressing, to be absorbed by the overlying compressed gauze.

Additionally, it is important that the dressing overlying a skin transplant may "breathe," that is to say, that the liquids absorbed by the gauze may evaporate into the atmosphere.

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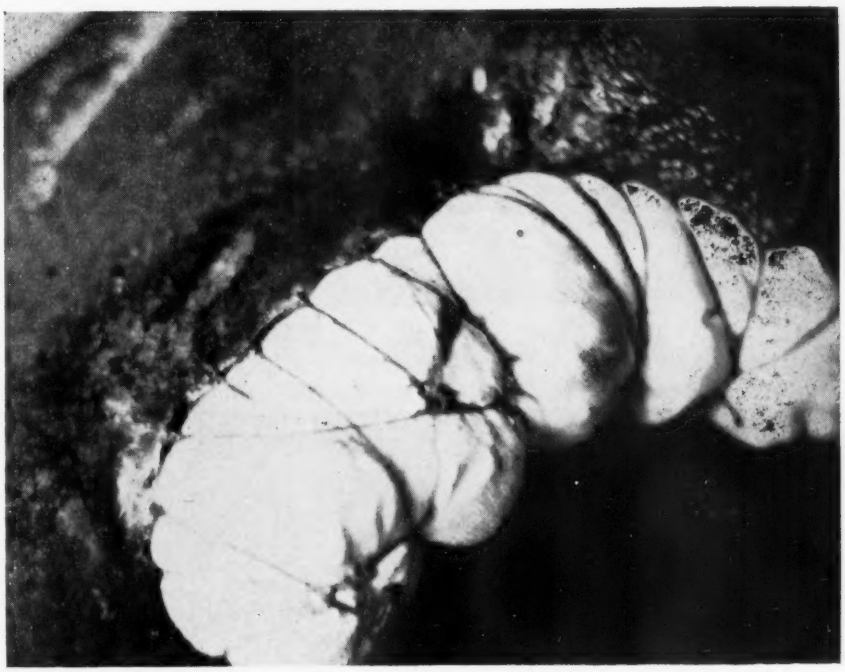
A.



B.

C.

Fig. 2 (Case 2).—*A*, *B*, and *C*, C. F., Mercy Hospital, operated upon Oct. 23, 1947; burn contracture of neck.

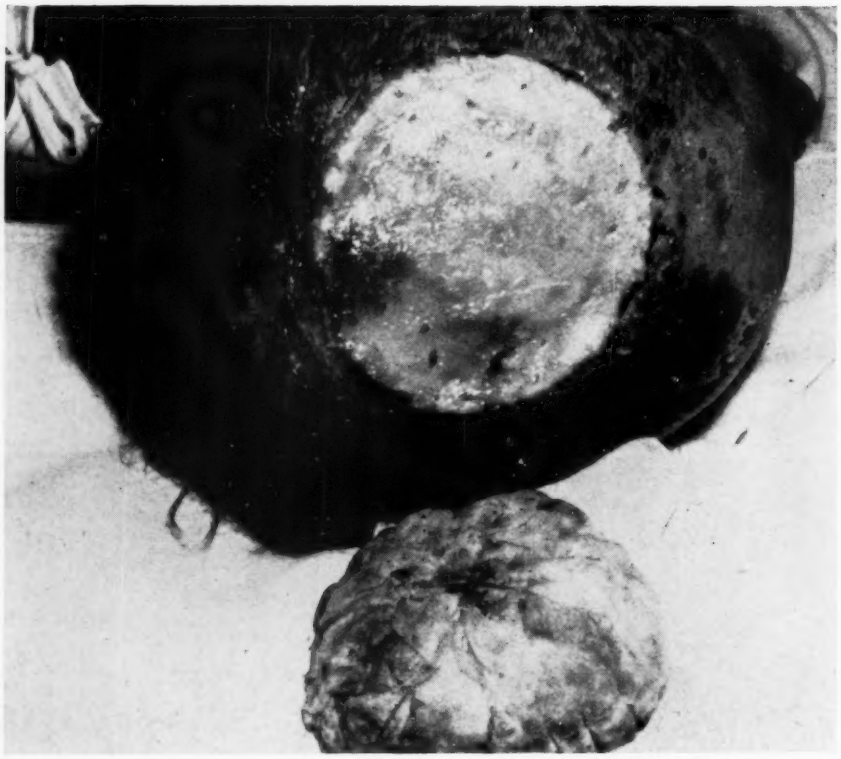


Fig. 3 (Case 3).—R. B., Wesley Hospital, operated upon May 14, 1947; basal-cell carcinoma of the scalp.

Fig. 4 (Case 4).—B. E. B., Mercy Hospital, operated upon Dec. 4, 1947; granulating burned area of dorsum of the hand.

If this function is not served by the dressing of the skin transplant, it will frequently macerate and undergo leucocytic digestion.

The onlaid gauze dressing is compressed evenly against the skin transplant. By use of the preserved long cotton sutures this compression is maintained. Apposition sutures are tied firmly across the crown of the gauze mass. This dressing is undisturbed for fourteen days. When it is removed a simple dry dressing is adequate mechanical protection to the firmly adherent skin transplant.

This technique provides uniform unyielding nonslipping absorbent compression and protection to a wide variety of skin transplants either half-thickness or full-thickness.

It is adaptable to a wide variety of recipient sites. It is particularly adaptable to sites that are concave and irregular such as illustrated in Case 1 (Fig. 1). This technique is particularly efficient in sites where it is difficult to accomplish compression by the usual annular compression dressing such as in the neck, as illustrated by Case 2 (Fig. 2). In a situation of this kind annular compressing dressings are faulty since by counterpressure they interfere with the veins in the the opposite side of the neck and if they pass under the arm they may embarrass the axillary nerves and vessels. If the dressings are wound tightly around the neck, swallowing and respiration are interfered with.

Scalp defects are readily surfaced using the tied-on compression dressing to hold full-thickness skin transplants in place. This is illustrated in Case 3 (Fig. 3). It is desirable to tailor these transplants to fit the defect exactly. Margin-to-margin approximation is important.

Case 4 (Fig. 4) illustrates one point and that is that this technique may be employed to hold split-thickness skin transplants in place over granulating surfaces.

The Padgett dermatome is essential in the accomplishment of an even-thickness autogenus transplant.

The development of this technique was a product of necessity. Upon returning to private practice two years ago, I found it impossible to secure a sufficient quantity of sea sponges. The few that were available were no larger than a tennis ball, of poor quality, and extremely costly. Mechanics waste and fluffed gauze have always given a less even and more infirm pressure dressing than sea sponges.

It is my opinion, based upon experience with the cases reported and others, that the tied-in-place onlaid gauze compression dressing gives better results when appropriately employed than do other forms of compression dressings.

Since this article was written it has been noted that a closely similar procedure was described in 1943, by James Barrett Brown and Frank McDowell in their *Skin Grafting of Burns*, page 92, published by J. B. Lippincott Company.

Case Reports

PARATHYROID ADENOMA

Occurrence in Father and Daughter

Thomas A. Shallow, M.D., and Kenneth E. Fry, M.D., Philadelphia, Pa.

(From the Samuel D. Gross Surgical Division of the Jefferson Medical College Hospital)

THE unique occurrence of parathyroid adenoma in father and daughter has not previously been reported. The father's case alone is of outstanding interest because he suffered two episodes of hyperparathyroidism separated by an interval of fifteen years. The unusual aspects of these two cases, as well as the long periods of follow-up obtained, warrant their report in some detail.

CASE REPORTS

Father's Case.—

First Episode.—C. F., a physician, aged 35 years, was seen in bed at home by one of us (T. A. S.) in November, 1931. At this time he was convalescing from spontaneous fractures of the surgical neck of the right humerus and comminuted intertrochanteric fractures of both femurs, sustained on Sept. 25, 1931, while walking up steps. The fractures had been reduced in Montgomery Hospital, Norristown, Pa. Studies done during this admission revealed a mild secondary anemia, occasional trace of albumin in the urine, and absence of Bence-Jones protein in the urine. The roentgenograms showed bone changes suggestive of osteitis fibrosa cystica or multiple myeloma.

Inquiry into the patient's past history disclosed that in 1922, at the age of 26 years, he had experienced symptoms of duodenal ulcer, proved by roentgenograms. In 1927, in addition to the gastrointestinal symptoms, he had polyuria and polydipsia of such severity that diabetes insipidus was suspected. In 1929 he became nervous and irritable. In 1931 his gait changed to what he described as a shuffle. In July of that year he began to experience a constant boring pain in all the extremities, worse at night. During the four-year period from 1927 to 1931 he lost forty pounds in weight.

Physical examination revealed a poorly nourished 35-year-old man obviously confined to bed because of multiple fractures. A mass was palpable in the region of the lower pole of the left lobe of the thyroid gland. The remainder of the physical examination was noncontributory. A presumptive diagnosis of parathyroid adenoma was made and operation advised.

The patient was readmitted to Montgomery Hospital on Dec 22, 1931. The previous laboratory studies showed no change, and the serum calcium was 13.0 mg. per 100 ml. Operation was performed on Dec. 23, 1931, using 1 per cent novocain local infiltration. A tumor was removed from the region of the lower pole of the left thyroid lobe. The sites of the other parathyroid glands were palpated but no enlargement could be detected. The patient's wound healed normally and he was discharged on the fifth postoperative day.

The gross and microscopic features of the tumor are shown in Fig. 1. It measured 3.3 by 3.2 by 3.1 cm. Microscopically, there was an encapsulated parathyroid adenoma composed of sheets of neoplastic cells supported by a well-vascularized, scanty connective tissue stroma.

During the ensuing year the patient's health gradually improved. The fractures united, he gained forty pounds in weight, and acquired his former vigor. He returned to active practice in June, 1933, and continued without symptoms until March, 1946.

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Second Episode.—The patient was admitted to Jefferson Hospital on May 1, 1946, at the age of 50 years. Within the preceding two months he had experienced increasing muscle weakness and fatigability, loss of ten pounds in weight, and pain in the upper third of the right arm. The pain was dull, boring, intermittent, lasting for one or two hours, and aggravated by activity. Despite these symptoms, he had continued work until admission.

Physical examination revealed a well-healed scar along the anterior margin of the left sternomastoid muscle. The thyroid was just palpable, but no nodules were felt. There was deep tenderness over the lateral aspect of the upper fifth of the right arm. The left lower extremity was two inches shorter than the right, with slight limitation of external rotation.

The blood count revealed a moderate secondary anemia. Urinalysis, except for a fixed specific gravity of 1.007 to 1.009, was normal. The blood urea nitrogen was 10.0 mg. per 100 ml. and creatinine 1.7 mg. per 100 ml. Urea clearance was 40 per cent of normal. Serum calcium was 15.8 mg. per 100 ml., serum phosphorus 2.1 mg. per 100 ml. and alkaline phosphatase 6.3 Bodansky units.

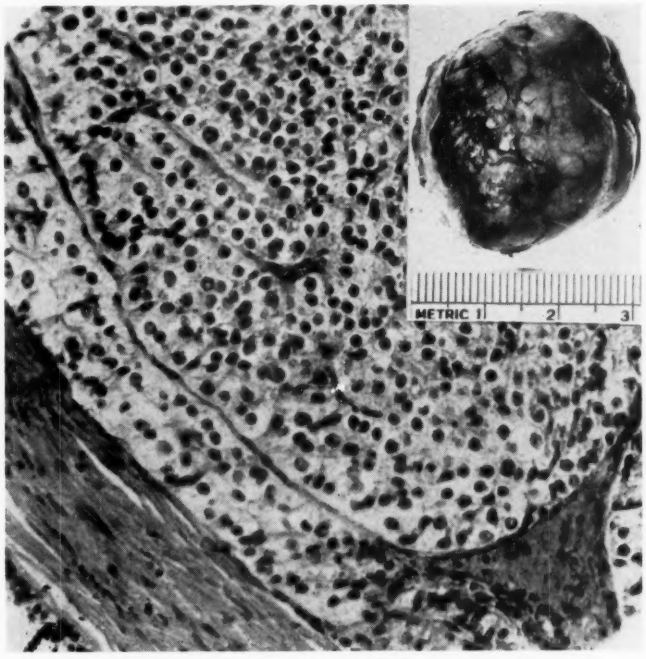

Fig. 1.—Gross specimen and microphotograph, oxyphil and chief cell adenoma of the parathyroid gland (×200).

Roentgenographic study of the entire skeleton revealed general demineralization of all the bones, with a grainy appearance of the calvarium. A large cyst was noted in the neck of the right scapula, as well as cystic areas in the right ulna, several ribs, the right femoral neck and trochanteric region, and left tibia. There was considerable aberrant calcification in both kidneys.

At operation, on May 16, 1946, using nitrous oxide-oxygen-ether anesthesia, the patient's thyroid region was explored. Exposure and palpation of the usual sites of the parathyroid glands, including the site of the previous adenoma, revealed no abnormalities. Substernal exploration disclosed a nodule to the right of the esophagus and behind the recurrent laryngeal nerve. The tumor was delivered after freeing the nerve which crossed its center.

On the first postoperative day the serum calcium was 9.6 mg. per 100 ml. and serum phosphorus 2.1 mg. per 100 ml. On the fourth day he first experienced tingling of the hands and mouth, a feeling of pressure in the anterior thoracic region, and mild shortness

of breath. The suspicion of incipient tetany was substantiated by a serum calcium of 7.7 mg. per 100 ml. The serum phosphorus was 3.2 mg. per 100 ml. On the eleventh day the serum calcium was 7.0 mg. per 100 ml. and serum phosphorus 3.6 mg. per 100 ml., despite the fact that the patient's symptoms were controlled by administration of calcium lactate and vitamin D. The patient was discharged June 1, 1946, on the sixteenth post-operative day. At this time the wound was well healed and the mild symptoms of tetany were easily abolished by oral administration of calcium lactate.

The gross and microscopic features of the tumor are shown in Fig. 2. It was well encapsulated and measured 4.2 by 2.6 by 2.3 cm. Microscopically, it was a parathyroid adenoma in which the neoplastic cells were of the water clear, chief, and oxyphil variety.

The patient failed to improve following discharge from the hospital. Appetite was poor, he lost weight, and the family noted a retardation in his memory and word aphasia. He experienced no symptoms of tetany, however, and a serum calcium determination on June 20, 1946, revealed 8.7 mg. per 100 ml.

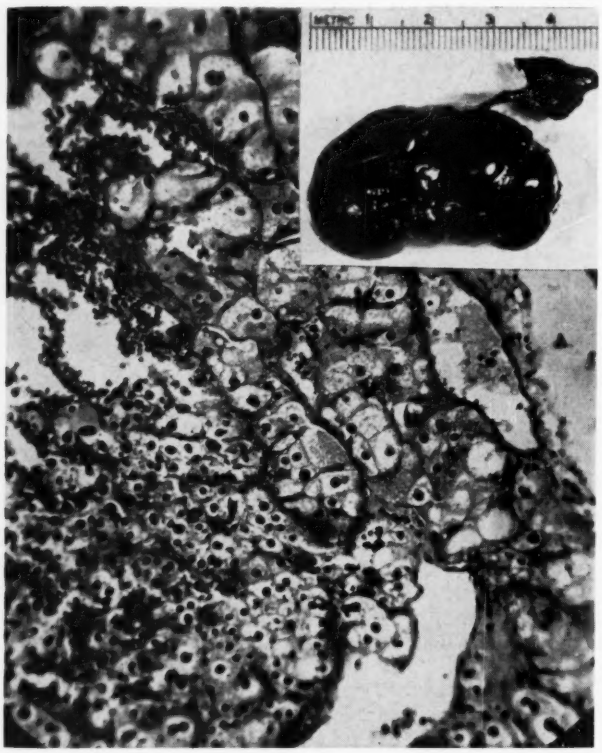

Fig. 2.—Gross specimen and microphotograph, adenoma of the parathyroid gland, mixed cell variety (×200).

The patient was readmitted to Jefferson Hospital in a state of stupor, July 10, 1946, on which day he vomited for the first time. The temperature was 101.2° F., pulse rate 94 per minute, and respirations 24 per minute. Detailed neurologic examination revealed no evidence of a localized lesion. The blood urea nitrogen was 40.0 mg. per 100 ml., creatinine 2.4 mg. per 100 ml., 30 per cent bromsulfalein dye retained at the end of 30 minutes, Van den Bergh positive direct with a serum bilirubin of 2.4 mg. per 100 ml., and serum amylase 400 units. Serum calcium was 6.0 mg. per 100 ml., serum phosphorus 6.5 mg. per 100 ml., and alkaline phosphatase 9.9 Bodansky units. Spinal fluid was under normal pressure and revealed no abnormalities.

The patient's condition improved following administration of fluids intravenously, glucose, protein, vitamins, and calcium lactate. On Aug. 23, 1946, the blood urea nitrogen

was 29.4 mg. per 100 ml. Appetite increased, he gained weight, and became clear mentally. He was discharged to his physician's care on Aug. 24, 1946. The patient died suddenly on April 20, 1947, from what appeared to be a cerebral hemorrhage. No autopsy was performed.

DAUGHTER'S CASE.—M. F., aged 14 years, was admitted to Jefferson Hospital on Aug. 1, 1939, with the chief complaints of loss of stamina and change of gait. Seven months prior to admission she began to experience increasing weakness after slight exertion. At the same time she gradually developed a change of gait, which was not improved by wedging of her shoes. One month prior to admission, the mother observed that the daughter's gait closely resembled the shuffling gait of the father eight years previously. Outpatient laboratory studies revealed that serum calcium was 15.4 mg. per 100 ml., serum phosphorus 1.8 mg. per 100 ml., and alkaline phosphatase 62 Bodansky units.

One year prior to admission the patient had sustained a fracture of the surgical neck of the left humerus following a severe fall. Roentgenograms at that time revealed no underlying bone disease, and the fracture healed normally.

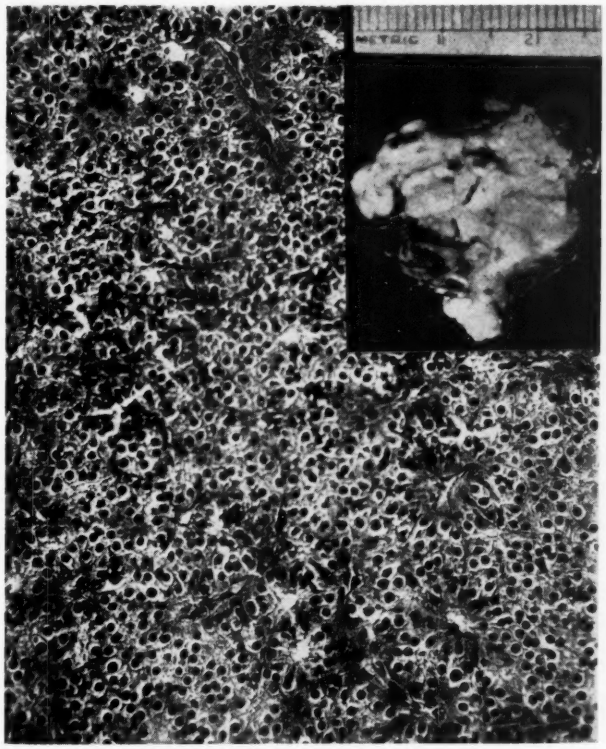

Fig. 3.—Gross specimen and microphotograph, adenoma of the parathyroid gland, predominately chief cell variety (×200).

Physical examination revealed that the patient had a myotonic gait, resembling the waddling of a duck. The remainder of the physical examination was negative, except that palpation in the region of the lower pole of the left thyroid lobe revealed a small, regular mass which moved with deglutition.

Repeat blood chemistry determinations were essentially the same as those just prior to admission. In addition, the blood count, urinalysis, urea clearance, blood urea nitrogen, and serum proteins were within normal limits. Roentgenologic study of the skeleton revealed demineralization of all the long bones and calvarium, with fuzziness and increased density in the metaphyseal regions.

At operation on Aug. 9, 1939, using avertin-nitrous oxide-oxygen and ether anesthesia, a parathyroid adenoma was removed from the region of the inferior pole of the left lobe of the thyroid. Careful palpation of the other parathyroid sites revealed no abnormalities.

On the sixth postoperative day the patient's serum calcium was 9.0 mg. per 100 ml., serum phosphorus 2.5 mg. per 100 ml., and alkaline phosphatase 17 Bodansky units. Repeat of these studies on the fourteenth day revealed a serum calcium of 9.5 mg. per 100 ml., serum phosphorus 2.7 mg. per 100 ml., and alkaline phosphatase of 125 Bodansky units. The patient's convalescence was uneventful, and she was discharged on the fifteenth day.

The gross and microscopic features of the tumor are shown in Fig. 3. It measured 2.7 by 2.5 by 2.2 cm. Microscopically, it was a parathyroid adenoma mainly of the chief cell variety, although there were a few small foci of oxyphil cells.

Complete follow-up examination of this patient on Nov. 10, 1939, three months after operation, revealed marked improvement. Gait had become normal, she had much more stamina, and was attending school regularly. Blood chemistry studies revealed a serum calcium of 10.2 mg. per 100 ml., serum phosphorus of 3.1 mg. per 100 ml., and alkaline phosphatase of 14.0 Bodansky units. Roentgenologic study showed definite remineralization of all the long bones, and the metaphyseal regions of the radius and ulna at the wrist joints were more normal.

On April 12, 1947, seven years and eight months after operation, the patient was again examined and in all respects was within normal limits.

DISCUSSION

In an analytical review of 322 cases of parathyroid adenoma by Norris,[1] collected from 1903 to 1945 inclusively, no mention is made of the occurrence of this tumor in members of a family. Although the development of the disease in our two patients in such close blood relatives may have been a mere coincidence, the possibility is at least suggested that in certain instances it might have a familial tendency. Schneider, Kyger, and McCullagh[2] recently reported its occurrence in second cousins once removed.

The father developed symptoms of parathyroid adenoma not long after the first reported surgical removal of a parathyroid adenoma by Mandl,[3] but was not operated upon until four years later following three spontaneous fractures. Removal of the adenoma in 1931 permitted such an improvement in his condition that he apparently was normal. The second adenoma, located substernally on the opposite side, did not produce symptoms for fifteen years. Whether the substernal adenoma was present at the time of the first operation in latent form and gradually became more active or whether it developed rapidly years later is uncertain. It is evident, however, that the hyperparathyroidism was primary and not secondary hyperplasia due to renal insufficiency. Renal damage was not manifest until the time of the second operation, fifteen years later. This was secondary to the hyperparathyroidism, as shown by roentgenologic demonstration of considerable calcification in both kidneys. At this time the blood urea nitrogen was normal, although the urine showed a low fixed specific gravity and the urea clearance was only 40 per cent of normal. With removal of the second adenoma the patient developed chronic tetany, hepatorenal failure, and died eleven months later from what appeared to be cerebral hemorrhage. The hyperphosphatemia developed on the basis of tetany and also phosphate retention on the basis of renal failure. Death from a vascular accident is in keeping with the disease because of the abnormal deposition of calcium

in the arteries. Although the history of the second episode dated back only two months, the irreparable damage caused by the disease is evidence that the hyperparathyroidism had probably existed insidiously and asymptomatically over a period of years.

It is interesting that the mother first suggested the diagnosis of parathyroid adenoma in the daughter because of the resemblance in gait to that of the husband in 1931. The fracture which occurred one year prior to the daughter's operation was probably not a pathologic one, since sufficient trauma was acknowledged and the roentgenogram showed no evidence of underlying bone disease. The subsequent roentgenographic findings were minimal, consisting chiefly of generalized skeletal demineralization. The prompt return of the blood calcium and phosphorus to normal following removal of the adenoma confirmed the diagnosis. The other siblings in this family showed no evidence of disturbance in calcium and phosphorus metabolism.

CONCLUSIONS

1. Parathyroid adenoma may occur in blood relatives. This suggests that in certain instances search should be made for evidence of disturbance in calcium and phosphorus metabolism in other members of the family.

2. Patients who have undergone surgical excision of a parathyroid adenoma should be checked periodically as long as they live, since it is possible for a second adenoma to develop.

The authors are grateful for the cooperation of Dr. Peter A. Herbut in reviewing the pathologic material.

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POLYPS OF THE SIGMOID OCCURRING THIRTY YEARS AFTER BILATERAL URETEROSIGMOIDOSTOMY FOR EXSTROPHY OF THE BLADDER

Report of a Case

Claude F. Dixon, M.D.,* and Rodger E. Weismann, M.D.,† Rochester, Minn.

TRANSPLANTATION of ureters into the rectosigmoid or sigmoid flexure of the colon has received universal acceptance in the past twenty years. There has been an increasingly wider application of some form of this operative procedure in the treatment of certain serious benign and malignant lesions of the lower part of the urinary tract. Late results are of considerable interest and importance in determining the ultimate usefulness of ureterosigmoidal anastomosis.

Advances in diagnostic and clinical methods of preoperative evaluation of both the urinary and gastrointestinal systems have aided in the proper selection of candidates for this type of operation. The operative morbidity and mortality have been sharply decreased since prophylactic and therapeutic use of the newer chemotherapeutic and antibiotic preparations and other valuable preoperative and postoperative measures. In recent years some workers have stated that bilateral ureterosigmoidostomy and total cystectomy can be accomplished in a one-stage procedure as safely as it formerly was in a three-stage procedure. It would seem, however, in most instances that the multiple-stage procedure is the safer.

Ureterocolonic anastomosis, as used in the surgical treatment of exstrophy of the bladder, was materially advanced by contributions of Maydl,[1, 2] Moynihan,[3] Bergenhem,[4, 5] Peters,[6] Coffey,[7] and Mayo[8] and associates.[9, 10] Its feasibility was demonstrated by these earlier investigators.[11] In the Maydl procedure, as modified by Moynihan, a portion or all of the trigone of the bladder with the ureterovesical valves anatomically intact, but with their nerve supply interrupted, is transplanted to the wall of the rectosigmoid. In the Bergenhem procedure, later modified by Peters, each ureter with a cuff of adjacent vesical wall is transplanted separately into the distal portion of the sigmoid. These two procedures have been almost entirely abandoned, not only because of technical difficulties, but also because of the vesical remnant which, as will be shown later, frequently may be the site of malignant change. The concepts and surgical principles originally described by Coffey have largely become the basis for the present-day surgical procedures. Many modifications[12] have been introduced which have reduced operative mortality and contributed to more satisfactory end results.

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POSTOPERATIVE CHANGES IN KIDNEYS

During the immediate and early postoperative phase, the presence of a serious ascending renal infection with subsequent renal insufficiency due to ureteral obstruction or atony, or both, formerly accounted for most of the operative morbidity and mortality after ureteral intestinal anastomosis. Some degree of pyelitis, ureterectasis, or both, usually was observed in the earlier series. In more recent reports Walters and Braasch[13] stated that little dilatation of the upper part of the urinary system should occur and, consequently, little infection. In seventy-six cases upon which they reported, only one death was caused by renal infection. In their follow-up study of seventy-nine ureteral transplants, Marshall and Gardner[14] reported that only four ureters failed to function properly after the patients were dismissed from the hospital. Ladd and Gross[15] reported that in twenty-six children operated on for exstrophy, only one child subsequently required nephrectomy for unilateral hydroureter and renal damage. Jidigian and Bickers[12] reported that of seventeen patients who survived ureterosigmoidal anastomosis, only one was readmitted subsequently for acute pyelitis.

In cases of ureteral transplantation for benign conditions, the outlook for good renal function over a period of many years is apparently good. Many of the patients who underwent the operation at the Mayo Clinic have been observed for more than twenty years.

POSTOPERATIVE EFFECTS ON THE COLON OR RECTUM

Except for the technical problems of anastomosis into the colon and those connected with the presence of myriads of pathogenic organisms in the contents, the sigmoid and rectum have not presented any serious obstacles to the development of the present operative procedures of ureteral colonic anastomosis. The distal part of the colon and the rectum are able to readjust remarkably well, in practically all instances, to the physical and chemical alterations of the contents occasioned by the constant influx of urine. Significant pathologic disorders of the bowel as a result of the presence of urine have apparently not been encountered heretofore. Furthermore, the incidence of diseases common to that portion of the bowel is not appreciably influenced by the presence of urine. There is no evidence that significant absorption of products of urinary excretion occurs from the distal part of the sigmoid or the rectum.[13]

The occurrence of glandular polyps in the sigmoid or rectum in a case in which unilateral or bilateral ureteral transplant into the distal part of the colon was accomplished is apparently extremely rare. In a careful search of the literature, we are unable to find a report of a case similar to ours. Hammer,[16] in 1929, reported a case of carcinoma of the sigmoid in a 60-year-old man who had undergone ureterovesicosigmoidostomy, after the method described by Maydl.[1, 2] The operation was done ten years previously for exstrophy of the bladder. The lesion in Hammer's case was probably primary in the transplanted vesical remnant. Reference will be made later to this report.

In 1919 Mayo[8] presented a remarkable series of twenty-six cases of exstrophy of the bladder in which the patients were operated on at the Mayo Clinic from

1912 through 1919. He employed a modification of the Coffey I technique. Operation was considered successful in twenty-two cases at the time of our report. The case we are reporting is one of this series.

The patient in the following case was recently observed and treated at the Mayo Clinic. Polyps were found in the sigmoid colon thirty years after successful bilateral ureterosigmoidostomy and cystectomy or exstrophy of the urinary bladder. The case is reported because of the unusual nature and importance of this complication.

REPORT OF A CASE

The patient, a single 33-year-old aeronautical research engineer, was first examined at the clinic on Sept. 20, 1916, at the age of 3 years. At the early admission he had exstrophy of the bladder and marked deformity of the penis and scrotum of a congenital nature. The only complaints were those associated with the nuisance of a constant flow of urine. On physical examination he was found to be an otherwise normal and well-developed child. There was typical exstrophy of the bladder with complete epispadias and a bifid scrotum containing both testes. Roentgenologic examination of the pelvis showed bilateral absence of the medial portions of the pubic bones. Concentration of hemoglobin was 7.4 Gm. per 100 c.c. of blood. Results of other laboratory tests were within normal limits.

On Sept. 27, 1916, the right ureter was transplanted into the bowel in the region of the rectosigmoid using the intraperitoneal Coffey I procedure. The left ureter was similarly transplanted on Oct. 14, 1916, into the upper sigmoid. On Oct. 21, 1916, excision of the mucous membrane and muscularis of the exstrophied bladder and portion of the abdominal wall was made. Convalescence from all three procedures was uneventful and the patient was dismissed from the clinic on Nov. 18, 1916.

Subsequently the patient developed normally. He was able to complete work for a degree in engineering from a university.

In 1941 he noticed attacks of pain in both costovertebral angles and flanks associated with chills, fever, and headache. These episodes continued to occur with increasing frequency and in the course of most of them he was hospitalized and given a course of sulfonamide therapy. In November, 1946, about one month prior to returning to the clinic, he had an acute attack of pain in both costovertebral angles with chills, fever, headache, and malaise. He was given a course of treatment with a sulfonamide and thereafter symptoms were relieved. He had two further similar less severe attacks during the interval before registration at the clinic on Dec. 24, 1946. Further investigation of his history revealed that he had observed some bright red blood in the stools in October, 1946, and that at that time he had consulted a proctologist who made a diagnosis of a small rectal polyp and advised its removal. The patient stated that he had had a rectal evacuation without associated symptoms approximately every three hours during the day but that prior to admission he had had occasional cramping pain in the lower midabdomen associated with bowel movements. In addition, he had lost approximately twenty pounds (9.1 kilograms) in weight.

Physical examination at the second admission revealed a well-developed man who did not appear particularly ill. There was slight tenderness in the left costovertebral angle. Bilateral lower abdominal paramedian scars of previous operations were present in the abdominal wall; there was fairly marked scarring and a herniation about 6 cm. in diameter in the suprapubic region at the site of excision of the exstrophied bladder. The persistent penile deformity consisted of a rudimentary duplicated glans and epispadias at the base. The scrotum was small and bifurcated but the testes were normal on palpation. With the exception of the presence of mild dilatation of the rectum no abnormalities were detected on digital examination of that structure. Proctoscopic investigation revealed a polyp on the right anterior wall of the rectosigmoid approximately 16 cm. from the anus.

Excretory urogram showed that the left kidney was nonfunctioning and that the right kidney was normal except for a mild horseshoe type of deformity.

Concentration of hemoglobin was 11.2 Gm. per 100 c.c. of blood, erythrocytes numbered 3,350,000, and leucocytes 6,000 per cubic millimeter of blood. The sedimentation rate was 81 mm. per hour (Westergren). The value for blood urea was 30 mg. per 100 c.c. A roentgenographic examination of the thorax revealed no abnormalities. Result of the flocculation test of the blood for syphilis was negative.

Because of the recurrent attacks of pain, chills, and fever and the loss of function of the left kidney, demonstrated by excretory urography, it was decided that left nephrectomy should be carried out. On Dec. 30, 1946, exploration of the left kidney was made through a left posterolumbar incision and it was found to be enlarged and thickened. A rather extensive inflammatory condition was present in the perirenal fat. At the site where the spermatic vessels crossed the ureter there seemed to be some angulation and partial obstruction. The ureter below this site was somewhat dilated but otherwise was in good condition. The kidney was removed; three ties were placed on the renal pedicle and one on the distal stump of the ureter. The pathologist reported that 15 cm. of ureter was removed with the kidney and that the kidney weighed 305 grams. The pathologic diagnosis was as follows: hydro-ureter, hydronephrosis, and chronic pyelonephritis. The postoperative course was uneventful. Dismissal from the hospital was given on the fourteenth postoperative day.

After the patient was released from the hospital, roentgenographic studies of the colon revealed two polypoid lesions in the sigmoid. The distal lesion was about 2.5 cm. in diameter and was thought to be the one observed previously in the course of proctoscopic examination. The proximal lesion was at the juncture of the sigmoid and descending colon; it was estimated to be about 7 cm. in diameter. Just orad to this tumor the roentgenologist found an annular constriction, the nature of which was not determined, but it was thought to be neoplastic. The remainder of the colon was normal. Further proctoscopic observations were made to a level of about 30 cm. above the anus but no lesion was found other than those previously demonstrated.

The patient was admitted to the hospital for preparation for a colonic operation. This preparation consisted of giving a residue-free diet, sulfasuxidine (succinylsulfathiazole) orally and daily colonic irrigations for four days. At the time of admission the concentration of hemoglobin was 13.2 Gm. per 100 c.c. and erythrocytes numbered 4,550,000 per cubic millimeter. On Jan. 31, 1947, exploration of the abdomen was carried out through a primary left rectus muscle-splitting incision. Two polypoid lesions were found in the sigmoid, as depicted by the roentgenologic studies. The liver, gall bladder, stomach, and remainder of the colon appeared to be normal. Palpation of the remaining right kidney revealed that it was enlarged to about one and one-half times normal size; the lower pole swung upward and mesially suggesting an incomplete horseshoe deformity. Through an antimesenteric longitudinal incision in the wall over the colon overlying it, the larger proximal polyp was delivered and excised with a portion of the mucosa and submucosa at its base. The stump of the left ureter attached to the descending colon just proximal to the lesion was identified. Exploration of the colonic mucosa at the base of the polyp, however, did not disclose the exact location of the orifice of that ureter. The bowel was closed transversely with two rows of chromic catgut suture. The smaller distal sigmoidal polyp was exposed in a similar manner just above the rectosigmoid. Before proceeding with excision of this lesion, the right ureter was identified and its site of transplant into the lower part of the sigmoid was carefully determined. It was found that the polyp arose in a mushroom fashion exactly at the orifice of the right ureter previously transplanted into the bowel. The pedicle was transected with much care with a probe in the right ureter. Hemostasis was obtained without difficulty by means of a carefully placed stick tie in the mucosa and submucosa of the colon about the ureteral orifice. The bowel was again closed transversely by means of two rows of chromic catgut suture; 5 Gm. of sulfathiazole and 100 Gm. of penicillin were left in the abdominal cavity before the wound was closed in layers.

The pathologist reported that the first tumor was a grade 1 adenocarcinoma in an adenoma, 4 cm. in diameter. The stalk of the adenoma was not involved. The second tumor was a hyperplastic adenomatous polyp, 2 cm. in diameter. The gross and histologic characteristics of the two lesions are shown in Figs. 1 to 3.

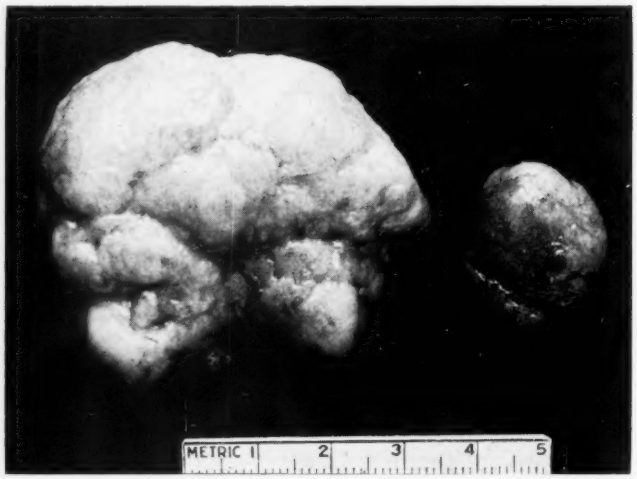

Fig. 1.—Two excised sigmoidal polyps; the larger is the proximal lesion and the smaller the more distal one.

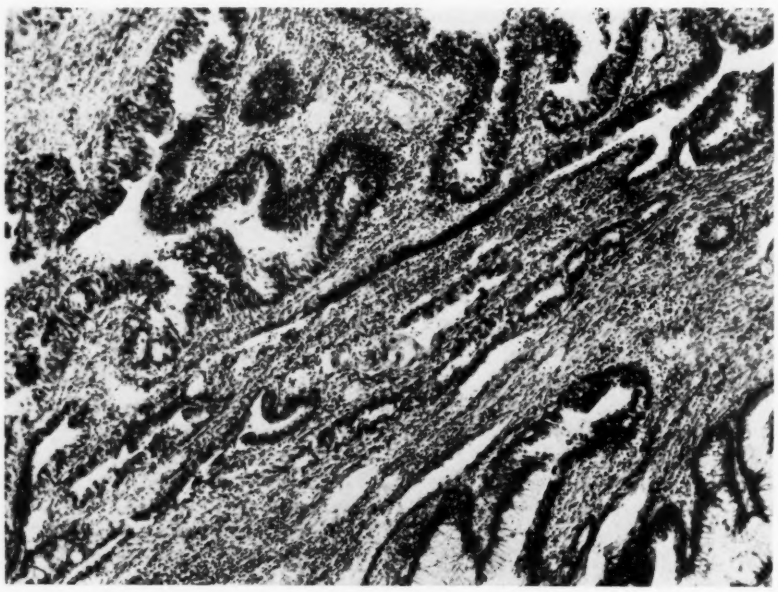

Fig. 2—The larger lesion; grade 1 adenocarcinoma in an adenomatous polyp (hematoxylin and eosin, ×55).

Postoperatively the patient was entirely afebrile. In the first twenty-four hours after the operation the urinary output per rectal tube was 650 c.c. and thereafter it ranged between 850 c.c. and 1,800 c.c. daily. Bowel movements of normal character and regularity were established by the eighth postoperative day. The patient resumed a residue-free

diet on the fifth postoperative day. At the time of dismissal from the hospital he was employing a full diet and colonic function was normal. On the eighth postoperative day a mild superficial wound infection developed and subsided within a few days under local treatment. Release from the clinic was on Feb. 21, 1947, at which time he was in good condition.

The patient reported by correspondence nine months postoperatively that he was in splendid health, had regained his normal weight, and was able to carry on his usual occupation and athletic activities.

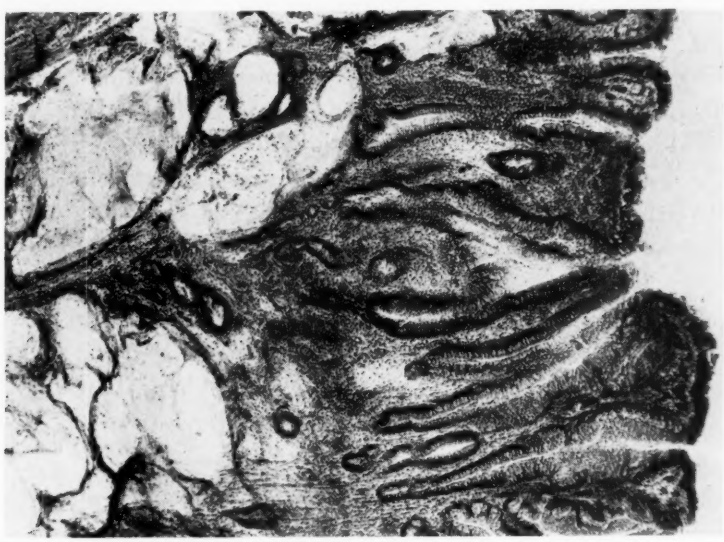

Fig. 3.—The smaller distal lesion; benign glandular structures in substance of the polyp and the surface covered with colonic epithelium (hematoxylin and eosin, ×25).

COMMENT

The presence of unilateral pyelonephritis, nonfunctioning kidney, and polypoid sigmoidal lesions is of considerable interest and significance in this case. Renal complications of this nature are, unfortunately, a common early postoperative development. On the other hand, loss of function in previously normal kidneys many months or years after ureterosigmoidostomy occurs much less frequently. Few long-term studies are available to ascertain with any certainty the incidence of very late renal complications. A check of the records of cases at the Mayo Clinic reveals no instance of proved loss of function in an undiseased kidney after dismissal following ureterosigmoidostomy.

The history in this case suggests that the pathologic changes in the left kidney may have been due to repeated episodes of ureteral obstruction, pyelonephritis, or both for a period of five years. The anatomic proximity of both sigmoidal lesions to the respective ureteral orifices would strongly indicate that one or both could produce enough intermittent complete or partial obstruction to account for the renal disease. It is likely that the proximal sigmoidal polyp, since it was the larger, was present for a longer period of time and had produced its mechanical effects on that portion of the sigmoid, involving the left ureteral opening. This is a probable explanation of why the left kidney showed the

evidence of disease. In the roentgenographic studies of the colon, the constricting defect, suggestive of an infiltrating neoplasm, apparently represented a localized temporarily intussuscepted area produced by the large polypoid lesion below it. However, there was no demonstrable pathologic process, as suggested by roentgenologic examination, proximal to this large polyp on exploration. A localized recurring intussusception involving the segment of sigmoid where the left ureteral transplant was located is considered an important mechanical factor in producing intermittent left ureteral obstruction and eventual serious damage to the left kidney.

In spite of considerable anatomic involvement of the orifice of the right ureter by the distal colonic polyp, there was, however, no evidence of significant amount of obstruction to the right ureter. There was no hydroureter on the right and the kidney felt normal, except for a slight congenital deformity in shape, to palpation at operation. It is interesting to speculate as to how much longer the right kidney and ureter would have remained normal.

The polyps which were seen in this case were similar to the adenomatous and carcinomatous polyps encountered in colons of many patients, with or without symptoms, and could not be distinguished histologically from the common solitary colonic or rectal polyps. It is of interest to note that the larger, and probably the older, contained regions of grade 1 adenocarcinoma which, in our experience, are present in the great majority of these lesions. It is assumed, therefore, that these neoplastic lesions arose from the colonic mucosa and could be expected to behave as lesions of that origin.

In Hammer's case, mentioned earlier, the carcinoma present appeared to arise from the implanted remnant of vesical wall and was thought to originate near the orifice of the left ureter. Metastasis was not demonstrable. Death was due to uremia with hydronephrosis on the left and pyonephrosis on the right. No surgical treatment of the sigmoidal lesion was attempted. The author pointed out the marked predisposition of mucosa of exstrophied bladder to the development of adenocarcinoma and the histopathologic similarity of adenocarcinoma of colonic origin and adenocarcinoma primary in anomalous glandular structures in the urinary bladder. Hammer, however, believed that the cancer in his case arose from the implanted tissue and secondarily involved the wall of the near-by sigmoid. In our experience the epithelium of the exstrophied bladder will eventually undergo malignant change in a large majority, if not all, of the cases. If that epithelium is transplanted, it appears to retain this tendency.

The association of the intussuscepting large polypoid lesion near the colonic orifice of a transplanted left ureter with a severely damaged and infected left kidney, occurring more than twenty-five years after a successful ureterocolonic anastomosis, is of considerable importance and has been extremely instructive to us. It is seen, then, that colonic lesions may occur which could seriously impair a completely successful ureterocolonic anastomosis. In cases in which evidence of obstruction to one or both of the transplanted ureters develops, particularly after many years have elapsed, a thorough proctoscopic and fluoroscopic investigation of the distal portion of the colon should be made. A history of

rectal bleeding or intermittent lower abdominal pain, related to bowel function, should strongly suggest the presence of a colonic lesion capable of obstructing an implanted ureter. Prompt treatment of the primary colonic lesion may allow satisfactory drainage of the upper part of the urinary tract and stop the destructive process in the kidney.

Transcolonic excision after transperitoneal sigmoidotomy[17] is considered entirely adequate for the eradication of the type of polyps encountered in this case. Should more extensive carcinomatous involvement of the wall of the distal portion of the colon be suspected, a more radical attack would be in order. Resection of the portion of the bowel containing the ureteral anastomosis would obviously entail another ureterosigmoidostomy, a cutaneous ureterostomy, or sacrifice of the kidney of the involved side. A colonic anastomosis would be required to remain unusually secure because of the urinary content of that segment of the large intestine. If reimplantation of the ureter into the colon is feasible, a site distal to the colocolostomy would be preferable. The anticipated risk of such extensive reconstructive procedures would be high. It would be useful to carry out this treatment in multiple stages, using a transverse complimentary colostomy.

SUMMARY AND CONCLUSIONS

A case has been reported in which a patient was successfully treated by bilateral ureterosigmoidostomy and excision of the exstrophied bladder, and returned thirty years later with an obstruction and infection of the upper left part of the urinary tract for which left nephrectomy was considered necessary. Examination of the colon revealed multiple polypoid lesions at or near the ureteral orifices, the one at the opening of the left ureter being the larger and undergoing early cancerous change. Transcolonic excision of both lesions was also performed and the patient made an uneventful recovery.

The circumstances encountered in this case have not, to our knowledge, been previously reported in the literature and represent a very unusual, but important, late complication of ureterosigmoidal anastomosis.

Thorough proctoscopic and roentgenographic study of the distal portion of the colon should be made in cases in which, many years after successful ureterosigmoidal transplantation, evidence of obstruction of the upper part of the urinary tract develops. Successful eradication of the colonic lesions may relieve the obstruction of the upper part of the urinary tract and, along with treatment of the infection of the urinary tract, may eliminate the necessity of carrying out nephrectomy.

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Erratum

In the November, 1948, issue of the JOURNAL, page 805, the article, "Surgical Management of Thoracic Duct Injuries," the cities following the authors' names are interchanged. The address of Dr. G. B. Hodge is Spartanburg, S. C., and the address of Dr. Hunter Bridges, now deceased, was Shreveport, La.

Editorial

Nitrogen Balance

WITHIN the past decade more and more attention has been given by surgeons to the nutritional deficiencies of surgical patients. It is now generally recognized that the patient whose nutritional deficiencies have been, in large part, corrected prior to operation will withstand the assault of anesthesia and operation better than one who is not so prepared. There remains, however, no unanimity of opinion regarding the methods best calculated to correct such deficiencies.

The study of the nutritional deficiencies in man has, in large part, centered around the protein imbalance which so many of these patients have suffered. It may well be that such intensive studies in a single direction have been correct, but all clinicians interested in this field must constantly remind themselves that nutritional deficiencies in man are usually of a complex nature.

One reads that "the metabolic needs of the patient have been met by the administration of 3,000 c.c. of a five per cent solution of glucose every twenty-four hours," an amount which provides but 600 calories a day, approximately one-third of the energy requirements of a patient at rest in bed. Regardless of the statement that the total calories in the diet are not very important, anyone who has studied the problem of undernutrition knows that the total caloric intake is important.

Time and again within the past five years, it has been stated that the protein requirements of the patient have been met because for short periods the patient has been "in positive nitrogen balance." This statement may, in reality, mean very little, for a positive nitrogen balance does not indicate positively that the nitrogen made available to the patient has been utilized to restore the depleted stores of tissue and plasma protein. Determinations of plasma protein concentration may mean very little under such circumstances, for these provide no concrete data which reflect the increase or decrease of the total plasma protein.

Certain of the substances being used to reinforce depleted protein stores are only slowly metabolized in the body following intravenous injection. Gelatin and serum albumin are conspicuous agents of this type and yet we are asked to believe that they too rapidly play a part in correcting a protein deficiency, while in reality they are stored for relatively long periods in the body before they become available for utilization in a nutritional sense.

A positive nitrogen balance means only that more nitrogen has been retained in the body on a given intake than has been excreted. It should not be made to imply that deficiencies in a nutritional sense have been corrected. If we are to continue to utilize the tools of the biochemist, we must learn how to use them and how properly to interpret the results, which our studies provide.

—*I. S. Ravdin.*

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

PRIMARY CARCINOMA OF THE LIVER

AN ANALYSIS OF FIFTY-FIVE AUTOPSIED CASES, THE RECORD OF A CASE WITH RESECTION, AND A REVIEW OF THE RECENT LITERATURE

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ALTHOUGH Rokitansky[113] distinguished between primary and secondary hepatic malignancy in 1849, it was not until 1876, when Kelsh and Kiener[69] reported two cases, that clinical details began to be recorded. The lapse between the pathologic and the clinical recognition of the disease can be chiefly attributed to Virchow's insistence that sites commonly affected by secondary neoplasms were only rarely the sites of primary growths.

Certain other landmarks are important in the history of primary carcinoma of the liver. In 1888, Hanot and Gilbert[55] classified the disease on a gross pathologic basis into nodular carcinoma, massive carcinoma, and carcinoma with cirrhosis. In 1901, Eggel[36] improved on this classification by distinguishing a multiple nodular form, a solitary massive form, and a diffuse form. In 1911, Goldzieher and von Bokay[50] classified primary hepatic malignancy histologically as hepatocellular and cholangiocellular, terms which are more precise than the nomenclature of hepatoma and cholangioma introduced by Yamigwa[157] in the same year. Later Ewing employed the term mixed tumor to indicate that both liver cell and bile duct cell carcinoma are present in the same neoplasm.

The surgical removal of a tumor of the liver was first attempted by Langenbüch[72] in 1888 and the first successful resection of a primary malignancy was accomplished by Lücke[78] in 1891. Keen,[68] in 1899, was apparently the first American surgeon to perform a successful resection.

Although primary carcinoma of the liver still presents many obscure and puzzling aspects, it can no longer be considered a rare neoplasm. When Eggel[36] reviewed the literature in 1901, only 163 cases had been recorded, and the validity of many of these was doubtful. By 1937 Charache[25] was able to collect 1,125 cases, 16 of which were eliminated as duplicates by Warvi[142] in 1944. Between Charache's report in 1939 and the present time (August, 1947), 452*

*Andriotakis and Cambylafka,[2] Armanino,[3] Berk and Lieber,[7] Berman,[10] Berns,[12] Bosé,[14] Boyd and Schlachman,[15] Cabot 26441,[17] Cabot 27362,[18] Cabot 31232,[19] Cabot 32201,[20] Cabot 32412,[21] Cabot 32422,[22] Clayman,[28] Croizet,[32] Cunningham,[33] Drummond and Tollman,[35] Feasby,[39] Gardner,[43] Gelfand,[44] Gnassi,[49] Gregory,[52] Hansen and associates,[56] Hartz,[57] Hentel,[58] Hermosilla Diaz and Sotomayor,[59] Hoyne and Kernohan,[63] Jenks and co-workers,[65] Joynt,[66] Keeler,[67] Liber and Brown,[74] Litman and Wells,[75] Liza and Hart,[76] Loesch,[77] Mathews,[84] Mensh and Hanno,[85] Morehead,[87] Mudgett and associates,[88] Neumann,[92] Quinland and Cuff,[94] Ortner,[98] Oshlag and associates,[99] Osterlin,[100] Packard and Stevenson,[101] Papahelius,[102] Pickrell and Clay,[104] Platou and Hill,[105] Pomeranz and co-workers,[107] Robiliard and Goldman,[112] Sanes and MacCallum,[117] Savard,[119] Steiner,[128] Tomlinson and Wolff,[134] Usuda and Uchida,[138] Warvi,[143] Webb,[144] Wentz and Kato,[147] Wilbur and associates,[150] Willis,[151] Woodlawn Hosp. C.P.C.,[155] Young.[159]

additional histologically proved cases of primary carcinoma of the liver have been placed on record. The various recorded series, with the 55 cases which form the basis of this report, bring the number of histologically proved cases now on record to 1,616.

The 55 cases mentioned are all autopsied material. Six were located in the files of Touro Infirmary in New Orleans between 1937 and 1944, and 49 were found in the files of Charity Hospital of Louisiana at New Orleans between 1928 and 1944, the last year for which complete autopsy proctocols are available in the record library at this time. In addition to a large number of cases classified in the Charity Hospital files as primary carcinoma of the liver on apparently sound clinical grounds, there have also been located at this institution 25 cases in which the diagnosis was made by inspection at exploratory laparotomy and 26 others in which it was made by biopsy under similar circumstances; 37 cases in which autopsy was performed but in which histologic examination was either not made or not recorded; 8 cases diagnosed by punch biopsy alone; and, finally, 2 cases in which the diagnosis was made on the clinical picture and the finding of malignant cells in aspirated ascitic fluid. No instances in which diagnosis was made by examination of a resected specimen were located. The 98 cases in which diagnosis was made by other methods than complete autopsy are not included in this discussion and will be reported separately.

INCIDENCE

It is impossible to speak definitively concerning the incidence of primary carcinoma of the liver for two reasons: (1) In the absence of uniform diagnostic criteria, numerous reported cases must be viewed with skepticism, though clinically, as in the cases discarded at the New Orleans Charity Hospital, there is little doubt that most of them were actual instances of the disease. (2) Official statistical records are of no value because tumors of the gall bladder, bile ducts, and liver are grouped under a single heading.

Race.—All the evidence indicates that primary carcinoma of the liver is most common in countries inhabited by the yellow-skinned and dark-skinned races. Composite autopsy reports from which regional incidences have been calculated (Table I) show that the disease is considerably more frequent in Asia and Africa than in Europe, with the exception of Greece, in which the frequency is greater than in Japan and China proper. The incidence in Italy (0.5 per cent) is also high in comparison with that of other European countries. The general incidence in Europe, however, is about the same as in America (0.20 to 0.26 per cent).

Reports which can be broken down into their racial components indicate that the Chinese continue to show a susceptibility to carcinoma of the liver even when they have changed their habitation. Hartz,[57] writing from Curaçao in the Netherlands West Indies, found 5 instances of carcinoma of the liver in 33 autopsies on Chinese subjects against only 4 instances in 1,350 autopsies on Negro and white subjects. Strong and Pitts,[130, 131] in a study from the Vancouver General Hospital, found 10 cases in 139 autopsies on Chinese subjects

TABLE I. AUTOPSY INCIDENCE OF PRIMARY CARCINOMA OF THE LIVER IN VARIOUS REPORTED SERIES

NON-AMERICAN SERIES				AMERICAN SERIES			
PLACE	NUMBER OF AUTOPSIES	NUMBER OF CASES	INCIDENCE (PER CENT)	PLACE	NUMBER OF AUTOPSIES	NUMBER OF CASES	INCIDENCE (PER CENT)
Formosa[138]	1,690	22	1.87	San Antonio[62]	200	3	1.5
Formosans, 14 in 502				Vancouver[130, 131]	1,967	12	0.61
Japanese, 8 in 1,188				Chinese, 10 in 139			
Java[8*]	8,253	109	1.3	White, 2 in 1,828			
South Africa[8*]	4,964	61	1.2	San Francisco[149]	11,045	49	0.44
Greece[102]	3,828	41	1.0	Detroit[8,* 43]	3,487	15	0.43
Japan[8,* 64]	43,832	421	0.96	Shreveport[84]	3,800	16	0.42
China[8*]	21,475	198	0.92	Omaha[8*]	1,100	4	0.36
Netherlands West Indies[57]	1,383	9	0.65	Buffalo[8,* 77]	7,400	26	0.35
Chinese, 5 in 33				Charleston[79, 151]	2,470	8	0.32
Others, 4 in 1,350				New Orleans	17,617	55	0.31
Italy,[8,* 26, 110]	43,058	216	0.5	New York[8,* 53, 76]	44,606	119	0.26
Philippines[8]	13,876	61	0.43	Boston[41, 115, 121]	12,029	28	0.23
Chile[32]	12,805	50	0.38	Baltimore[8,* 29, 33]	28,923	63	0.21
India[8*]	7,234	23	0.32	Washington[92, 143]	10,017	20	0.20
Hungary[50]	6,000	18	0.30	Minneapolis[8*]	1,500	3	0.20
Switzerland[8*]	2,800	6	0.21	Rochester[63]	16,303	31	0.13
England[8,* 30]	44,083	83	0.19	Chicago[8,* 128]	12,945	24	0.11
Holland[8*]	2,936	5	0.15	Iowa City[8*]	5,100	1	0.02
Germany[8*]	171,712	191	0.11				
†Racial Elements:				†Racial Elements:			
Eastern	92,360	834	0.87	American	180,509	478	0.26
African	4,964	61	1.2	Negroes	7,765	34	0.44
European	274,417	560	0.2				
Central & South American	14,188	59	0.41				

[8*]Berman's Collected Review Figures.

†Calculated from the series listed above.

against 2 cases in 1,828 autopsies on white subjects. Wilbur and his associates[150] reported from San Francisco 19 instances of the disease in Chinese in a total of 49 autopsied cases. In view of the relatively small number of Chinese in America (77,504 out of a total population of 133,217,064, according to the 1940 census), the relatively large number of cases of primary carcinoma of the liver reported among them by Wilbur and his associates as well as by a number of other observers seems significant.

It is also possible that Negroes, when they leave their native habitat, carry with them a predisposition to the disease,[8] though the tendency is not as clear-cut among them as it is among the Chinese. The disease is relatively frequent in Africa. Bergeret,[6] who supplied no basic figures, stated in a report from Dakar that primary carcinoma of the liver constituted 57 per cent of all carcinomas. Berman,[8] who reported an incidence of 30.7 per cent for malignant disease in the general Bantu population, found that when the analysis was limited to carcinoma in adult male workers in the Witwatersrand gold mines whose ages ranged from 16 to 40 years, carcinoma of the liver comprised 90 per cent of the total number of cases. Primary hepatic malignancy has been reported to represent 18.7 per cent of all carcinomas in the semi-Bantu races who inhabit the west coast of Africa.[8]

Reports which emphasize the racial aspects of the disease are surprisingly few in America, and no studies have been reported from the South, where, according to the 1940 census, the Negro population represented 24 per cent or more of the population in each of nine states. A compilation of reports from the United States, in which the racial components were clear, revealed a composite autopsy incidence for primary carcinoma of the liver in Negroes of 0.44 per cent, which is somewhat higher than the incidence of 0.26 per cent calculated for the general population. According to Kennaway,[70] the available data supply no evidence that the American Negro is especially susceptible to the disease.

The Charity Hospital of New Orleans probably cares for the great majority of Negroes in Louisiana, where colored persons comprise 35.9 per cent of the population. The autopsy figures, which can be broken down only after 1937 (Table II), reveal a smaller incidence of Negro than white, although the Negroes slightly outnumbered the white people in hospital admissions between 1928 and 1944. The number of cases of primary carcinoma of the liver is, however, too small for much emphasis to be placed upon such calculations. The six cases reported from Touro Infirmary were all in white subjects, since that institution treats only white inpatients.

TABLE II. AUTOPSY INCIDENCE OF CARCINOMA OF THE LIVER AT CHARITY HOSPITAL OF LOUISIANA IN NEW ORLEANS

CATEGORIES	TOTAL CASES	CARCINOMA OF LIVER	PROPORTION
Autopsies 1928 to 1944	15,737	49	0.31
Autopsies 1937 to 1944	6,760	26	0.38
White	2,674	12	0.45
Negro	4,086	14	0.34
Male	3,990	21	0.53
Female	2,770	5	0.18

Sex.—The doubts occasionally expressed concerning the true racial incidence of primary carcinoma of the liver[70] do not exist concerning the sex incidence, which is predominantly male. All reports bear this out. Berman's[8] figures for the Bantu races show the male-female ratio to be 7:1. Ninety-four per cent of Bergeret's 157 cases occurred in males.[6] There was only one female in the 134 Chinese patients with the disease reported by Tull.[135] Twelve of Cunningham's[33] 14 patients were males, as were 47 of the 49 patients reported by Wilbur, Wood, and Willett,[150] 14 of the 16 reported by Matthews,[84] 12 of the 14 reported by Loesch,[77] and 59 of the 67 reported by Gustafson.[53] All of Lynch's six (Negro) patients were males,[79] as were 51 of the 75 patients under 16 years of age reported by Steiner.[127]

The same male predominance is evident in the cases observed at the New Orleans Charity Hospital, where 36 of the 49 cases which make up the series occurred in males. Fourteen of the 22 white patients and 22 of the 27 Negro patients were males. Since the Negro female admissions were higher than the white female admissions, the disproportionately low incidence in Negro females may be significant. Five of the 6 cases analyzed at Touro Infirmary occurred in men.

Age.—Primary carcinoma of the liver has been reported at all ages. The range in the 49 Charity Hospital cases was from 4½ months to 85 years, both the youngest and the oldest patients being white. The age distribution was about what would be expected for any malignant neoplasm, the greatest concentration of cases (36) occurring during and after middle life (between 41 and 70 years) but no age being immune. The most significant point concerning the age incidence is the apparent tendency of the disease to occur earlier in Negro than in white subjects. Seven of the 10 patients in the series who were under 40 years of age were Negroes. This tendency is in accord with the age incidence in other reports. In Berman's[8] study of the disease in the Bantu, for instance, 82.6 per cent of the patients were under 40 years of age.

Primary carcinoma of the liver is relatively frequent in youth. Noeggerath[93] in 1854 observed a case in a newborn child, and Widerhofer[149] reported a case in a 3-day-old child. Tomlinson and Wolff[134] in 1942 were able to collect 82 authentic cases in persons under 16 years of age. Eight cases in the same age group have since been reported in the literature,[2, 74, 87, 88, 101, 105] and the addition of the 4 cases observed at Charity Hospital brings the total to 94.

Sex and Age in Relation to Pathologic Process.—The predominance of primary carcinoma of the liver in the male sex has been explained as due to the higher incidence of cirrhosis of the liver, while in the female the occurrence of the disease is explained by the frequency of biliary tract infection.[41] The rather frequent statement that liver cell carcinoma tends to develop in the male and bile duct cell carcinoma in the female is not entirely borne out by the statistics. Eggel[36] found 57 per cent of the cholangiomas in his series in women, and 6 of the 11 cholangiomas reported by Hoyne and Kernohan[63] occurred in this sex, but only 2 of the 8 cholangiomas reported by Cunningham[33] occurred in women. In the Charity Hospital series 24 of the 29 cases of liver cell carcinoma occurred in males, as did also 9 of the 13 cases of bile duct cell carcinoma.

The statement is also frequently made that bile duct cell carcinoma occurs at a later age than liver cell carcinoma. The Charity Hospital series supports this observation. The age differential was particularly marked in colored patients, in whom the average age for liver cell carcinoma was 44.8 years, as compared with 58.2 years for bile duct cell carcinomas. In white subjects the difference was not significant.

ETIOLOGY

The etiology of primary carcinoma of the liver, like the etiology of carcinoma in other locations, remains to be clarified, though certain factors seem to offer at least a partial explanation of its occurrence.

Cirrhosis.—Of all presumably predisposing conditions, cirrhosis is most frequently incriminated, and the association is too striking to be explained away as merely coincidental, though it is impossible to determine accurately the number of cases of hepatic cirrhosis which are followed by primary hepatic malignancy. Various reports state the incidence to be from 2.8 to 54.5 per cent. Hepatic malignancy occurred in 90, or 4.5 per cent, of 1,989 cases of hepatic cirrhosis collected by Berk and Lieber,[7] while in 1,073 cases of primary carcinoma of the liver collected by the same writers, cirrhosis was present in 658, or 61.3 per cent. In Berman's[11] collected series the association was noted in 73 per cent of cases, while in his personal series it was noted in 79.6 per cent. Wilbur and his associates[150] found hepatic cirrhosis present in 26 of 49 cases of primary carcinoma of the liver. In the Charity Hospital-Touro Infirmary series cirrhosis was present in more than 70 per cent of all cases (Table III) and was considerably more frequent in males than in females.

TABLE III. INCIDENCE OF CIRRHOSIS IN PRIMARY CARCINOMA OF THE LIVER IN RELATION TO THE TYPE OF MALIGNANCY AND THE SEX DISTRIBUTION

	MALES		FEMALES		TOTAL		
TYPE OF MALIGNANCY	TOTAL CASES	CASES WITH CIRRHOSIS	TOTAL CASES	CASES WITH CIRRHOSIS	MALE AND FEMALE	CASES WITH CIRRHOSIS	PERCENTAGE
Liver cell	24	23	5	2	29	25	86.2
Bile duct cell	9	3	4	2	13	5	38.4
Mixed cell	4	2	1	1	5	3	60.0
Undifferentiated	4	4	4	2	8	6	75.0
Total	41	32	14	7	55	39	70.9
Percentage	Males 78 per cent		Females 50 per cent		Total 70.9 per cent		

Cirrhosis is more likely to be associated with liver cell than with bile duct cell carcinoma. Gustafson[53] stated the respective incidences as 54.1 and 33.3 per cent. In Hoyne and Kernohan's[63] series cirrhosis was associated with 75 per cent of the liver cell carcinomas but with only 18 per cent of the cholangiomas. In our cases (Table III) cirrhosis was considerably more frequent in liver cell than in bile duct cell carcinomas.

Opinions differ as to the relationship between hepatic cirrhosis and primary carcinoma of the liver. In cirrhosis a hyperplastic, compensatory process occurs in specialized liver cells in response to a demand for increased functional activity,[89] but whether some particular irritant or an actual carcinogenic factor

initiates a malignant change in the proliferative tissue is not yet known. Carli[23] believed that three possibilities must be considered: (1) Cirrhosis may precede the malignancy and play an etiologic role. (2) It may occur concomitantly, as a result of the same irritative process responsible for the malignancy. (3) It may develop as the result of the neoplastic change. Still another possibility is that the underlying changes in hepatic cirrhosis, which are an increase in connective tissue associated with damage to and loss of liver cells, serve merely as an important prerequisite for carcinomatous change. Whatever the train of events, the association, as has been pointed out, is frequent and it is sometimes extremely striking, as in the case reported by Mensh and Hanno,[86] in which cirrhosis was known to have been present for eight years before carcinomatous changes were observed in the liver with metastases to the osseous system.

Laennec's (portal) cirrhosis is the type of cirrhosis usually associated with primary carcinoma of the liver. When hemochromatosis is present, the cirrhosis is usually of the pigmentary type; yellow atrophy cirrhosis (Mallory's toxic cirrhosis) is only occasionally observed.[29, 79] Some observers[115] consider that the role of the latter varieties is of more importance in the etiology of primary carcinoma of the liver than the role of portal cirrhosis.

Willis[151] was of the opinion that in hemochromatosis the liver is inherently cancerous; primary hepatic carcinoma was present in three of his seven cases of hemochromatosis, and Berk and Lieber,[7] who found the association in 3 of 15 cases, were of the same opinion. Hemochromatosis was present in all 6 cases of primary carcinoma of the liver reported by Lynch,[79] all of which occurred in the Negro. Stewart,[129] on the other hand, found the two diseases associated in only 14 of 120 cases (11.6 per cent), while Sheldon[122] thought that the association was at the most not more than 6 or 7 per cent, and concluded that primary carcinoma of the liver was no more apt to occur in organs which were the site of hemochromatosis than in those in which the more usual nonpigmentary variety of cirrhosis was present. In 436 collected cases of hemochromatosis there were 32 cases of primary carcinoma of the liver,[7] or 7.3 per cent, which seems to support Sheldon's point of view.

Alcohol.—The possible relationship between alcohol and cirrhosis of the liver is no part of this discussion, though it should be remembered that it may exist. Some investigators,[109] however, have suggested that alcohol, especially among the more primitive races, may play some part in the production of hepatic malignancy by supplying sufficient irritative and noxious influences to produce carcinomatous changes in a cirrhotic liver. The alcohol imbibed from an early age by certain Bantu in Africa is particularly powerful, and the speculation seems warranted that some relationship may exist between the noxious effects of alcohol consumed by primitive races and the high incidence of primary hepatic malignancy among the young people of those races. A definite history of alcoholism was obtained in 10 of the 55 patients in the Charity Hospital-Touro Infirmary series.

Chronic Irritation.—Chronic irritation is known to be an important etiologic factor in the production of carcinoma in certain organs of the body. Cholelithiasis, for instance, is present in most cases of carcinoma of the gall bladder.

The same reasoning has been applied to the etiology of primary hepatic carcinoma. Sanes and MacCallum[117] reported two cases of hepatolithiasis associated with carcinoma of the intrahepatic bile ducts, and Armanino[3] reported a case of carcinoma of the liver in a 17-year-old boy in which it was thought that the carcinomatous changes were initiated by the presence of a choledochus cyst and the resulting changes in the biliary tract and the liver. Pomeranz and his associates[107] also advanced the theory that chronic infection of the gall bladder with cholelithiasis may contribute to the production of adenocarcinoma of the intrahepatic bile ducts.

Parasites.—Parasitic infestations of the liver have been suggested as etiologic factors in primary carcinoma of the liver, on the ground that they cause hepatic irritation and damage. All the parasites which may infest the liver have been implicated at various times.[11, 109] That parasites play a part in the production of cirrhosis seems reasonable, but even in parts of the world in which both hepatic parasitic infestations and primary hepatic carcinoma of the liver have their greatest incidence a true cause and effect relationship remains to be demonstrated.

Syphilis.—Spirochetal infection has been mentioned as a possible etiologic factor in primary carcinoma of the liver,[38] and there is no doubt that syphilis may play a part in the production of an antecedent cirrhosis. Moreover, syphilis and hepatic malignancy are frequently associated, especially in dark-skinned races. Syphilitic lesions of the liver are, however, seldom found at autopsy. In the 55 cases which make up the present series, the blood serology was positive only 6 times, and too much significance must not be attached to these cases, since false-positive reactions are fairly frequent in carcinoma of the liver.

Congenital and Hereditary Factors.—Slye's[124] work has clearly shown that in mice hereditary factors are responsible for the production of hepatic neoplasms. No such proof exists for the development of the disease in human subjects, although in some of the more frequently affected races a hepatic tumor diathesis has been postulated, analogous to the genetic constitution which predetermines the incidence of carcinoma in certain strains of rats.

Pepere[103] has suggested that all solitary adenomas of the liver are congenital, and congenital malignant adenomas have been described by Ewing[37] and by Ribbert[111] and others. Strong support has been given to the thesis that in the newborn infant and in young children, neoplastic changes readily occur, as a result of congenital maladjustment of liver cells.[37] Cirrhosis is seldom seen in association with primary carcinoma of the liver in patients under 16 years of age, as Steiner[127] has pointed out, and Mudgett and associates[88] have also advanced the opinion that teratoid carcinomatous growths in very young children can best be explained on a purely congenital basis. Muir maintained that hepatic adenomas undergoing malignant changes often arise from displaced cells, but adequate proof remains to be adduced. Teratomas, from which hepatic cancers may arise, are known to result from developmental abnormalities. It is doubtful that congenital maladjustment of liver cells with a predisposition to cancer formation explains many cases of primary carcinoma of the liver in

adults, but the explanation, as Ewing contended, may be of much more significance in youth.

Trauma.—Crawford,[31] among other writers, has cited cases of primary carcinoma of the liver in which trauma was thought to be a possible etiologic factor; in fact, the malignancy was believed to have been precipitated by an abdominal injury. The possibility cannot be entirely discounted, but the number of cases in which the association existed is still small and the element of pure coincidence must be kept in mind.

Dietary and Nutritional Factors.—Probably the most important advances in the investigation of the etiology of primary carcinoma of the liver concern possible nutritional factors. It seems something more than coincidence that the greatest incidence of the disease is in those countries and among those races in which the diet is poorly balanced and generally inadequate. Among the Bantu of South Africa, where, as has been pointed out earlier in this paper, primary carcinoma of the liver is a frequent disease, hepatic cirrhosis is observed in approximately four of every five patients who come to autopsy. The staple diet of this race consists chiefly of corn meal and fermented milk. Meat is a luxury which is only occasionally possible. The diet is therefore high in fat, low in protein, and extremely deficient in vitamins. Gilbert and Gillman,[45, 46] who fed this staple diet to young rats, were able to produce marked fatty changes in the liver, with associated cirrhosis. Hepatic neoplasms have also been observed in experimental animals fed for long periods of time on diets which favor the development of cirrhosis.

The evidence strongly suggests, as Rusch and Brumann[116] saw it, not that cancer is the result of a deficient diet or that certain diets induce the development of cancer—since neoplastic development and growth depend on many factors—but rather that primary carcinoma of the liver may be frequent in peoples of Asia and Africa because their diets are lacking in certain factors essential for a defense mechanism against malignancy. Whatever the relationship, hepatic cirrhosis, hepatic malignancy, and the elements of the diet seem closely associated, and the diet is perhaps of more importance, according to evidence now available, than any other recognized contributory factor.

Experimental Evidence.—An extended discussion of the experimental production of cancer is beyond the scope of this communication, but certain studies related to primary carcinoma of the liver must be briefly mentioned.

Most important of the chemical agents now under investigation are the azo compounds, notably O-amino-azotoluene and P-dimethyl-amino-azobenzene. If these agents are incorporated in the diet fed to rats and mice, a well-marked cirrhosis develops, which may progress to cancer formation.[13, 97] If, however, the same diet is fortified with a large quantity of protein and vitamin B complex, the development of hepatic carcinoma is greatly delayed. If the diet is kept deficient in these elements, the rate of cancer formation is increased. The evidence thus suggests that adequate dietary elements may protect the liver cells against carcinogenic agents. The effects of 2-acetylamine fluorene are similar to those of dimethyl-amino-azobenzene. It is more difficult, however, as

Bielchowsky[13] showed, to inhibit carcinogenesis in rats by an adequate diet when the former agent is used.

The malignant changes produced by carcinogenic agents occur subsequent to cirrhotic changes, though the evidence suggests that cirrhosis is not an essential precursor.[96] On the other hand, as Orr[97] demonstrated, the yield of malignant tumors is greater when it occurs.

Considerable attention has been devoted to the effect of diet on artificially produced hepatic malignancy. Opie[96] demonstrated that rice actively factors carcinogenesis, while Sugiuri and Rhoads[132] showed that cirrhosis and cancer produced by dimethyl-amino-azobenzene could be completely inhibited if 15 per cent of the diet consisted of yeast. Opie showed that the appearance of hepatic carcinoma in experimental animals was greatly accelerated by a fatty diet of low protein content, and White and Edwards[148] made the same observations in connection with cystine and methionine. Sugiuri obtained partial inhibition of malignant hepatic tumors by the use of dried whole milk, with which he also reported the successful treatment of cirrhosis. Riboflavin has been shown to have an inhibitory effect on carcinogenesis.

Dietary inclusions and deficiences do not affect all artificially produced hepatic neoplasms in the same manner. Thus tumors induced by 2-acetylamine fluorene were not influenced by variations in the protein content, while those produced by dimethyl-amino-azobenzene were definitely affected.[13]

Intrahepatic Carcinogenic Factors.—Several writers, among them Schabad,[120] Des Ligneris,[34] Hieger,[61] Steiner,[128] and Sannie,[118] have suggested the existence of a carcinogenic factor in the human liver. According to Steiner and Des Ligneris this factor is present in apparently normal persons as well as in those with carcinoma somewhere in the body. Des Ligneris, whose studies were conducted among Bantu, showed that this presumptive factor is present to a greater degree in this race than in the white race, though, according to Steiner,[128] it is no more common in the American Negro than in white subjects. These facts raise the question whether the difference between the American and the African Negro is on a constitutional or on an environmental basis; in Steiner's[128] opinion the carcinogen is present in the Bantu as the result of environment and not because of any racial disorder of metabolism.

CLINICAL PICTURE

The statement is frequently made that the clinical course of carcinoma of the liver is not characteristic and that the clinical characteristics of the disease differ from case to case. The statement is not precisely correct. The rapidly fatal course of events is unfortunately all too characteristic. Furthermore, certain symptoms and signs appear in combination fairly frequently, though it must be granted that they are in no sense pathognomonic either individually or collectively. Clinical classifications have, however, been worked out by Berman,[9] Ewing,[37] and Gustafson,[53] and a comparison of important reported series with the series reported in this communication (Table IV) indicates that certain clinical findings tend to be prominent in many cases.

Symptoms.—Abdominal pain, which was present in 37 cases, was the most important symptom in this series, as it is in all reported series (Table IV), and

was likely to be the first symptom noted by the patient. In this series it was the first symptom in 26 cases. It was usually situated in the epigastrium and right hypochondrium and was usually of a dull, persistent character, never being severe enough in itself to force the patient to seek immediate medical attention. A history of acute attacks of severe pain was seldom present, even in association with hematemesis, which was entirely painless in 4 of the 6 cases in which it was observed. Severe pain, in contrast, was experienced in the cases of intraperitoneal hemorrhage, which variously occurred as the result of a breakdown of, or hemorrhage into, a subcapsular nodule, or as the result of rupture of esophageal varices into the peritoneal cavity.

TABLE IV. COMPARATIVE DISTRIBUTION OF CLINICAL FINDINGS IN VARIOUS REPORTED SERIES OF PRIMARY CARCINOMA OF THE LIVER

CLINICAL FINDINGS	NEW ORLEANS (55 CASES) (PER CENT)	MAYO CLINIC (31 CASES) (PER CENT)	SAN FRANCISCO (49 CASES) (PER CENT)	CINCINNATI (37 CASES) (PER CENT)	COLLECTED SERIES (500 CASES) (PER CENT)
Abdominal pain	67	87	72	71	52
Distention	58	87			
Weight loss	42	71	52	94	88
Weakness	25	87			
Nausea, vomiting	35	45		44	12
Jaundice	44	58	60	80	34
Pedal edema	44	74	42	40	60
Dyspnea	44				
Hepatomegaly	84	58.1	77	91	68
Palpable mass	33				
Hepatic tenderness	27			15	17
Fever	49	39		52	34
Ascites	54	77	60	37	48
Distended abdominal veins	25	26			
Splenomegaly	5	19			
Anemia	31		22	97	68
Gastrointestinal bleeding	11		14		
Pulmonary signs	31				
Delirium, coma	18				

In 5 instances the pain was described as "indigestion" and was thought to bear some relationship to the ingestion of food, though as a rule pain and digestive disturbances were not related. Pain in the scapular regions, the back, and the lumbosacral region was complained of by 8 patients, in 2 of whom it was the first symptom. Abdominal pain was not present in any of these cases.

Abdominal distention was complained of by 26 patients, in 24 of whom it was the first symptom. It was usually of gradual and insidious onset. Twenty-four patients, 15 of whom were Negroes, complained of dyspnea, which was the first symptom in 8 cases. This is apparently a more important symptom than the literature would suggest. It was associated with ascites in 13 cases, but the association obviously does not explain all cases.

Loss of weight was complained of during the course of the disease by 23 patients, but was the first symptom in only 5. The average weight loss was between ten and twenty-five pounds, but losses of as much as forty pounds were recorded. Emaciation, however, was more likely to be a terminal than an

initial finding. Asthenia, malaise, and anorexia, though they are often stated to be major symptoms in carcinoma of the liver,[9] occurred in only 19 of the 55 cases in this series and were the first symptoms in only 4.

Nausea and vomiting occurred during the course of the illness in 19 patients but were the first symptoms in only 3. Frank hematemesis occurred in 6 cases, in all of which it was a terminal fatal event. In only one other case was the vomitus described as bloody or of the "coffee-grounds" variety. Diarrhea was complained of by 9 patients and constipation by 4, but in no instance was either a first symptom.

Jaundice was present in 11 patients, only 3 of whom were Negroes, but was reported as a first symptom by only 4. It is not unusual, of course, for jaundice to be overlooked by Negro patients and by their families, or, for that matter, by dark-skinned white patients. It was eventually present in 24 cases in the series, but was usually a terminal, or at least a late, sign.

Swelling of the feet was complained of by 17 patients, 6 of whom listed it as a first symptom, but on examination it was found to be present in 7 other patients. It was bilateral in all instances. In 2 cases the edema extended from the feet into the scrotum.

Delirium, without excitement but passing into coma, occurred in 10 patients as a terminal event from which none recovered. In one case coma was associated with hemiplegia and led to a diagnosis of cerebral vascular accident, but autopsy revealed nothing pathologic in the cerebrum. In one case reported by Zeller and Mallory[21] the patient presented a positive Babinski sign and spastic, followed by flaccid, paralysis, but at autopsy no pathologic process could be demonstrated in the central nervous system. The authors pointed out that symptoms referable to the central nervous system, which often are quite marked, may accompany hepatic insufficiency. The clinical picture is analogous to that observed in uremia, in which symptoms referable to the central nervous system are prominent clinically but in which only minimal nonspecific lesions are found in the brain at autopsy.

Earlier studies of carcinoma of the liver indicate that fever is common in this disease. This was not true in the Charity Hospital-Touro Infirmary series. It was noted in 27 cases, in 2 of which it was a first symptom, but it was usually a terminal event which followed a characteristic pattern, the temperature rising from a previously normal level in a sudden, steplike elevation which heralded the approaching exodus. Terminal rises of 105 and 106° F. were not uncommon, but temperature elevations, if they were present earlier in the course of the illness, were intermittent and seldom exceeded 101 or 102° F. The septic type of temperature which was occasionally observed could usually be explained by the finding at autopsy of central hepatic necrosis, often associated with cavity formation.

Physical Findings.—By far the commonest finding on physical examination in the Charity Hospital-Touro Infirmary series was enlargement of the liver, which was noted in 46 patients, although tenderness was associated in only 18 cases. The enlargement amounted to only 3 cm. in some cases, but in

others the liver extended down into the pelvis. The hepatic enlargement was sometimes not apparent on the first examination because of the presence of ascites, which was readily demonstrable on physical examination in 30 cases. After paracentesis the edge of the liver could not infrequently be palpated considerably below the umbilicus.

Although its surface was frequently described as nodular, a definite mass arising from the liver was noted in only 15 cases, in 2 of which the finding of the mass was the first evidence of illness. Dilated abdominal veins were present in 14 cases; usually they appeared only above the umbilicus and often they extended up into the chest. Small telangiectatic areas were occasionally noted on the back or in the scapular regions.

Signs of pulmonary involvement, ranging from coarse râles to massive consolidation, were noted in 17 cases. The findings were highly suggestive of metastases, but definite evidence on this point could not be established in any case merely by physical examination. In 9 cases it was possible to demonstrate a raised, fixed lobe on the right side of the diaphragm, this number not including upward enlargements of the liver in which the diaphragm was not fixed.

The spleen was palpable in 3 cases, and in 3 other cases purpuric manifestations were present in the form of small petechial cutaneous hemorrhages.

PATHOLOGIC PROCESS

Macroscopically it is not possible to distinguish between liver cell and bile duct cell carcinoma, the final diagnosis always resting with the pathologist. It was possible, however, on gross examination to divide 51 of the 55 cases into three pathologic groups: (1) local massive carcinoma, (2) local nodular carcinoma, and (3) diffuse nodular carcinoma. In some instances local massive carcinoma appeared in combination with one or the other of the nodular types, most often the diffuse nodular type.

The liver was found to be greatly enlarged on gross inspection at autopsy in 25 cases. The average weight was 2,290 Gm., but the range was from 1,200 to 7,000 Gm. Often the enlargement was extremely irregular. One of the lobes, most often the right, was likely to be greatly enlarged while the left and caudate lobes were small. In all instances massive enlargement of a single lobe could be accounted for by the presence of local massive carcinoma. The largest livers, however, were the sites of diffuse nodular neoplasm, the numerous nodules of which had replaced most of the normal liver tissue.

Local Massive Carcinoma.—Local massive carcinoma, in which a single large nodule was present in one lobe or in which a multitude of smaller nodules had coalesced to form a large nodule, was found in twelve cases. In nine instances a single large nodule was present, usually in the right lobe; in the remaining cases local nodules were also present. In some cases the entire right lobe had been replaced by a massive carcinoma derived from the confluence of smaller nodules.

The consistency of the tumor masses depended upon the amount of secondary change which had occurred. Sometimes they were firm; frequently

they were quite soft, because of the presence of liquefied matter. In this type of carcinoma necrosis was frequent and hemorrhage into the nodule not uncommon. Often a cavity filled with yellow, cheesy, sometimes bloodstreaked material suggested a possible liver abscess. Berman was of the opinion that tumors of soft consistency were of the rapidly growing type. Necrosis in nodules near the surface of the liver was frequently associated with adhesions between the diaphragm and the hepatic capsule, and the omentum, stomach, and intestines were also often adherent to the liver.

Local Nodular Carcinoma.—Local nodular carcinoma, in which two or more nodules were present in a circumscribed area, was found in six cases, in three of which the nodules were found in association with massive carcinoma. In all three cases the local growth was present in one lobe of the liver and the massive growth in another. As a rule, a few nodules, ranging in size from a pea to a pigeon's egg, occurred close to each other in a single area of the liver. Sometimes Glisson's capsule was raised by nodules near the periphery and small irregular bosses could be palpated. In other instances the surface of the liver was smooth and palpation furnished no intimation of the serious disease process present within the substance of the organ. On section the nodules were usually found to be fairly firm and whitish gray. They were often bile-stained but were seldom hemorrhagic. Secondary changes were also infrequent.

It is quite possible that local nodular carcinoma represents simply an intermediate process between a single local malignant nodule and the diffuse nodular variety of the disease. The local nodules may eventually coalesce to form a single massive tumor or may metastasize within the liver and present as a generalized nodularity.

Diffuse Nodular Carcinoma.—Diffuse nodular carcinoma was present in 33 cases, in 13 of which it was associated with massive carcinoma. The liver was often bizarre in shape; one or two lobes or the entire organ being riddled with innumerable nodules of all sizes, shapes, color, and consistency. The smaller nodules tended to be located toward the periphery, though small nodules were often found circumscribing larger nodules in the depths of the hepatic substance. Larger nodules were likely to be necrotic and often consisted of little more than a shell. Smaller nodules were likely to be hard and gritty.

Hemorrhage was frequent in this type of case, as was hemoperitoneum, as the result of rupture of necrotic nodules near the surface of the liver. In a number of cases differentiation between the nodular and the massive form of carcinoma was difficult, for coalescence of nodules appeared to give rise to several massive tumors. Whether the massive form developed first and gave rise to secondary nodules or whether the nodules appeared first and coalesced to form the massive type of neoplasm is open to speculation.

HISTOPATHOLOGY

Liver Cell Carcinoma.—Carcinoma arising from liver cells in this series conformed, in general, to the structure of normal hepatic architecture. The tumor cells were large, ranging in size from 5 to 20 microns and were polygonal.

They were arranged in cords or trabeculae, usually to a thickness of two to ten cells, separated from each other by a very fine stroma with abundant vascular elements. These sheets of cells sent fingerlike projections into normal liver tissue and surrounding connective tissue. Scattered nests of irregularly arranged cords were not uncommon.

The cells frequently had large round hyperchromatic nuclei. Often the nucleus practically filled the cell, leaving only a fine ring of cytoplasm at the periphery. It was often vesicular and finely granular, and a well-marked chromatic network was visible. Nucleoli were usually seen.

The cytoplasm of the neoplastic cells was characteristically granular, and either fine or coarse. Bile pigment was often seen within the cytoplasm, which was occasionally described as foamy. Not infrequently, cells with vacuolated cytoplasm could be seen in areas farthest from the blood supply. Mitotic figures were extremely common, while giant cells, some with as many as ten to fifteen nuclei, abounded in the area of the neoplastic cells.

Necrosis, hemorrhage, and hyaline degeneration were frequent. Normal liver cells near areas of neoplastic cells were small and granular and often showed marked fatty degeneration. In some cases in this series they were compressed by rapidly growing malignant cells, so that their shape was bizarre and they presented pressure atrophy and necrosis. In some areas an attempt at cell regeneration was observed, with both tumor cells and hyperplastic liver cells present in the same lobule. Regeneration of cells was frequently striking, the new liver cells usually being arranged in the form of small nodules surrounded by fine strands of periportal fibrous tissue. The stroma between the cords of tumor cells was of the finely vascular type. It became coarser toward the periphery and eventually took the form of cirrhotic strands surrounding the tumor nodules. Newly formed blood vessels were abundant and attempts at bile duct formation were frequent. Free tumor thrombi were frequently observed within the lumina of blood vessels and sinusoids.

Round cell infiltration, which was common, was particularly frequent in tumors associated with fairly well-marked portal cirrhosis. Polymorphonuclear leucocytic infiltration was occasionally observed.

Cholangiocellular Carcinoma.—In cholangiocellular carcinomas the histologic picture was characterized by groups of cells aggregated into definite alveolar or acinar formation, sometimes tending to form pseudoglands. The cells were usually columnar but were often of the cuboidal epithelial type, although irregular shapes were not uncommon. The nuclei, which were markedly hyperchromatic, were usually situated at the base. The cytoplasm was clear. Mitotic figures were seldom seen, though mitosis was much more frequent in cases in which a wild disorderly growth occurred in dense connective tissue toward the periphery of a nodule. Giant cells were also not often seen.

In contrast to the liver cell type of hepatic malignancy, avascularity of the stroma was the prominent feature in cholangiocellular carcinoma. The connective tissue consisted of dense thick cords, with very few blood vessels. Newly formed bile ducts were present in moderate numbers. Lymphocytic infiltration into the connective tissue was occasionally observed.

Mixed Cell Carcinoma.—In five cases histologic examination showed characteristic features of liver cell and bile duct cell carcinoma in the same growth. Herxheimer[60] and Fischer[40] advanced the hypothesis that bile duct cells are transformed into liver cells in neoplasms originating from bile duct cells. Muir[90] and Rolleston[114] took the opposite position and traced bile duct cell formation from liver cells. Many authors,[4, 82, 145, 153] considered that some tumors might be of dual origin and presented both varieties of cells. Whatever their origin, these cholangiohepatomas, to use Warvi's[142] nomenclature, or mixed tumors, to use Ewing's,[37] are apparently not common.

Histogenesis.—Up to this time the origin of hepatic carcinoma has not been established. Advocates of the multicentric theory contend that numerous primary foci of liver cell cancer can arise simultaneously or in succession in the same liver by the transition of hyperplastic liver cells into malignant cells, and that a similar metamorphosis occurs in bile duct cells. Advocates of the unicentric theory, on the other hand, contend that there is but one primary nodule and that all secondary nodules arise from it by simple intrahepatic metastasis, spread being accomplished by early invasion of the portal blood vessels. On the surface, the latter theory seems the more reasonable.

METASTASES

Extrahepatic metastases, according to Greene,[51] Charache,[25] and others, are relatively infrequent in primary carcinoma of the liver and considerably less frequent than in carcinomas elsewhere in the body. The series reported in this communication does not bear out these opinions: In 40 of the 55 cases, 72.7 per cent, clear-cut evidence of spread beyond the liver was found at autopsy (Table V). Metastatic lesions to the number of 120 were found in 22 different sites. Ewing,[37] in line with the opinion expressed by Liza and Hart[76] that liver cell carcinomas tend to metastasize via the blood stream and bile duct cell carcinomas via lymphatic channels, stated that hepatomas metastasize more often than cholangiomas. In this series, 23 of 29 hepatomas had metastasized beyond the liver, as had 9 of 13 cholangiomas, 2 of 5 mixed tumors, and 6 of the 8 tumors in which histologic differentiation was impossible. Metastases from hepatomas numbered 72 and were found in 19 different sites. Metastases from cholangiomas numbered 22 and were found in 8 different sites. Metastases from tumors of undifferentiated cell types numbered 19 and were found in 22 different sites, and metastases from mixed cell tumors numbered 7 and were found in 6 different sites.

Metastases to the regional lymph nodes (porta hepatis, mediastinal, mesenteric, gastrohepatic, periaortic, and retroperitoneal lymph nodes) and to the lungs were most frequent. The right lung was more often affected than the left. Pulmonary metastases would be expected, since carcinoma of the liver can spread by way of the blood and the lymph stream as well as extend directly through the diaphragm and spread by contiguity. In a few cases a bloody pleural effusion was observed on the right side, in the absence of metastases in the pleura or the lung. Mallory,[17] who reported similar observations, expressed

TABLE V. DISTRIBUTION OF METASTASES IN PRIMARY CARCINOMA OF THE LIVER

SITES	NUMBER OF CASES WITH METASTASES	PROPORTION OF ALL (40) CASES WITH METASTASES
Lymph nodes	27	67.5
Thoracic		
Lungs	27	67.5
Diaphragm	5	12.5
Pleura	3	7.5
Intra-abdominal		
Omentum	6	15.0
Peritoneum	5	13.5
Intestinal wall	3	7.5
Gall bladder	3	7.5
Adrenal glands	3	7.5
Kidneys	2	5.0
Cul-de-sac	2	5.0
Pancreas	1	2.5
Mesentery	1	2.5
Spleen	1	2.5
Cardiovascular		
Hepatic vein	10	25.0
Portal vein	7	18.5
Inferior vena cava	7	18.5
Right auricle	2	5.0
Bone		
Ribs	2	5.0
Vertebra	1	2.5
Abdominal wall		
Anterior	1	2.5
Posterior	1	2.5
Skin	1	2.5

the opinion that a fairly free passage of fluid could take place to the right pleural cavity through the diaphragm. In one of the three instances of pleural metastases no secondary nodules were found in the lung.

It is rather surprising that metastases were not more often present in the omentum (Table V), for in many cases it was adherent to the liver in the region of large necrotic nodules, especially in instances of local massive carcinoma with necrosis. Generalized peritoneal seeding was observed in only one of the five cases in which peritoneal metastasis had occurred. In two of the three cases in which the intestinal wall was infiltrated, the spread could be explained by direct extension, because the hepatic flexure in one instance and the jejunum in the other were attached to the liver by adhesions in the region of necrotic nodules.

Secondary nodules were present in the cul-de-sac twice, their presence in each instance probably being due to cancer cells which had dropped from liver nodules into the pouch. In one of these cases the peritoneum and omentum were the site of metastases, but in the other no intra-abdominal secondary nodules could be identified. The spleen was affected in only one case, which does not seem to bear out Liber and Brown's[74] suggestion of a possible lymphatic spread from the liver to the spleen.

In all five cases in which metastases were found in the diaphragm the extension was presumably direct, the diaphragm being adherent to the liver in the region of malignant nodules. It is surprising that this structure, like the omentum, is not more often the site of metastatic growths.

Bony metastases occurred in three cases, twice to the ribs and once to the thoracic vertebra. In one instance the skin over the lower right costochondral junction was the site of metastasis. There was no instance in this series of the type of metastasis in which a Horner's syndrome is produced by the presence of secondary nodules in the lowest cervical vertebra and the sympathetic ganglion. In a case of this sort described by Cabot[18] the clinical picture simulated that associated with Pancoast's tumor, as the result of a large metastatic nodule in the apex of the lung.

Metastatic nodules in both bones and lungs have frequently been reported to show bile formation.[92] This phenomenon was observed in some pulmonary metastases in this series but not in any instance of osseous metastasis.

Malignant thrombi were present in the veins in several cases in this series. They were present in the hepatic vein in ten cases, in many of which histologic examination of sections of the vein showed that the presumed thrombi were actually metastases to the venous wall.

The portal vein contained malignant thrombi in seven cases, in each of which ascitic fluid was present, though it was bloody in only two instances. Gelfand[44] considered that portal thrombosis explained the presence of bloody or serosanguineous ascitic fluid in primary carcinoma of the liver, though, as this series demonstrates, the ascitic fluid is not necessarily bloody when portal thrombosis is present. According to Mallory,[20] hypernephroma involving the renal vein and the vena cava is the only neoplasm in addition to hepatoma which ordinarily extends into the veins in the form of gross thrombi.

In two of the seven cases in this series in which thrombi were found in the inferior vena cava, large thrombi were also found in the right auricle, definitely attached to areas of infiltration in the auricular wall. Simpson,[123] Gregory,[52] and Rowen and Mallory[115] have all pointed out that such an association is extremely infrequent. According to Gregory,[52] thrombi in the inferior vena cava should be suspected if dilated superficial veins are present in the anterolateral portion of the thorax and the abdomen; their presence in this location was noted in five of the seven cases of inferior vena cava metastases in this series. In only one instance, however, was pain in the back associated with a thrombus in the inferior vena cava; this association was first pointed out by Pleasants[106] in 1911. Clinically, severe dyspnea, jugular engorgement, and a sudden increase in the amount of ascites are often associated with thrombosis of the inferior vena cava with extension to the right auricle, though no such association was observed in this series.

COMPLICATIONS AND COINCIDENT DISEASES

Hemorrhage is the most serious complication of primary carcinoma of the liver. Sometimes it takes the form of a slow ooze from an area in the periphery of the organ. At other times it occurs as a massive, fatal loss of blood, the clinical manifestations of which suggest an acute abdominal condition (Berman's "acute abdominal cancer");[9] numerous instances are reported in the literature, though the Charity Hospital-Touro Infirmary series contains none.

This type of hemorrhage usually occurs from a necrotic nodule projecting from the surface of the liver and is the result of erosion of a large hepatic vessel by the malignant growth.

In addition to its association with hepatic cirrhosis and other conditions which may play an etiologic role, primary carcinoma of the liver has been reported in association with diabetes mellitus,[28, 66] purpura,[95] and hypoglycemia.[91] In all reported cases of hypoglycemia, sufficient normal liver tissue remained to maintain normal liver function and normal glycogen storage.

Hansen and his associates[56] reported a case of primary carcinoma of the liver in a 10-year-old child in which marked lipemia was associated with extreme osteoporosis and great bony deformity. The authors explained the osteoporosis as due to defective retention of calcium and phosphorus by the osseous system. Since the food intake was adequate, and since no defect of absorption could be demonstrated, it was concluded that osseous metabolism, which in some way was bound up with liver function, was perverted in this way by the malignant growth. Wood[154] reported a case of generalized xanthomatosis associated with primary carcinoma of the liver in an infant. No similar cases seem to be on record.

DIAGNOSIS

The diagnosis of primary carcinoma of the liver is not a simple matter because, as has been pointed out, the clinical picture is not characteristic. Diagnosis is, however, of great urgency, for the disease is so rapidly fatal that treatment must be instituted without delay if it is to be of any avail.

The procedures by which diagnosis can be made will be instituted only if it is constantly borne in mind that the disease may exist. Such symptoms, therefore, as abdominal pain and distention, loss of weight, dyspnea and edema of the ankles in the absence of cardiac disease, enlargement and tenderness of the liver, and signs of portal cirrhosis should lead to the suspicion of carcinoma of the liver in all persons over the age of 40 years. In younger persons a palpable mass in the region of the liver should be regarded as neoplastic until it is proved not to be.

Laboratory Studies.—Laboratory studies should be carried out routinely, for they may help to exclude other diseases of the hepatobiliary system, but they do not supply much useful diagnostic information. The white blood cell count will exclude leucemia and infectious states; in this series it ranged from 4,000 to 15,000 per cu. mm. The red blood cell count usually reveals some degree of anemia, which is not usually severe. Hematocrit readings, or, better, blood volume estimates may give a truer picture. In this connection the studies on chronic shock by Clark and his associates[27] are of interest. They show that in malnourished patients with malignant disease a depleted blood volume often masks the presence of severe anemia.

Blood sugar estimations are unlikely to reveal hypoglycemia unless the liver is seriously disorganized by the malignant growth. If cirrhosis is suspected, serum protein determinations may be useful. In the Charity Hospital-Touro Infirmary series the serum protein values were normal or only slightly

lowered, though the albumin-globulin ratio was rather frequently reversed. Icteric indices are usually not very high, even when frank jaundice is present; the highest reading in this series was 150. If pathologic bone conditions can be excluded, an elevated alkaline phosphatase is suggestive of obstructive disease of the liver. In Gutman's[54] studies with this test, primary carcinoma of the liver was always associated with values of more than 10 Bodansky units.

Tests of liver function should be carried out in all cases but should be interpreted with caution, for the physiologic properties of the liver are such that it can be extensively invaded by a malignant growth or other disease processes while the functional values remain normal or close to normal. If this possibility is borne in mind, information of value may be secured from tests of prothrombin values, the hippuric acid excretion test, the bromsulfalein excretion test, the cephalin-flocculation test, the tyrosine test[73] and the blood amylase test.[125] Somogyi[125] stated that remarkably low values were secured by the blood amylase test in persons with hepatic damage; in his own experience the test had many times directed attention to pathologic changes, later confirmed at autopsy, before they were apparent clinically.

The Takata-Ara reaction is reported to be useful in differentiating between intrahepatic carcinoma and extrahepatic carcinoma (of the bile ducts and pancreas), when jaundice is present. According to Stein,[126] the reading is negative in carcinoma of the pancreas and of the extrahepatic ducts without hepatic metastasis and positive in jaundice due to extensive primary carcinoma of the liver. In his experience the negative reaction was correct in 19 of 19 cases and the positive reaction correct in 9 of 10, which suggests that the test is of definite though limited value in the differential diagnosis of jaundice.

Roentgenography.—Roentgenography may be extremely useful in primary carcinoma of the liver in revealing such suggestive findings as esophageal varices, hepatic enlargement, masses in the hepatic area with elevation and fixation of the diaphragm, and localized bulges in the diaphragm. Elevation of the diaphragm, without the pleural reaction seen in subdiaphragmatic abscess, was stressed as an important diagnostic sign by Hermosilla Diaz and Sotomayor.[59] Garcia Capurro[42] pointed out that hepatic tumors arising from the anterior border of the left lobe tend to cause anteroposterior displacement of the stomach, while tumors arising elsewhere in the liver may cause displacement of the esophagus posteriorly and to the left, with resulting difficulties in the passage of food. Pomeranz and his associates[107] suspected primary carcinoma of the liver when a "selective" barium residue is found at the lesser curvature of the stomach, near the left hepatic lobe.

Visualization of the liver by thorotrast is a useful procedure which is not, however, free from risk. Moreover, thorotrast is a radioactive substance which, according to MacMahon and his associates,[80] may be capable of initiating malignant changes.

Roentgenograms of the chest should be made, to exclude possible metastases. Urography and perirenal insufflation of air should be carried out to exclude possible hypernephroma, and the biliary tract should be visualized. Finally, the

stomach and large bowel should be examined with an opaque medium to exclude carcinoma in those locations.

Peritoneoscopy.—Peritoneoscopy, which permits direct visualization of the liver, has its greatest field of usefulness in differentiating between hepatic cirrhosis and hepatic malignancy. It is also of value, if the clinical evidence is confusing, in determining operability in borderline cases, though the decision to withhold operation should be made with the greatest caution.

Aspiration and Biopsy.—Aspiration of ascitic fluid, with microscopic examination, sometimes reveals malignant cells. The method is therefore useful in distinguishing between a malignant process and hepatic cirrhosis or ascites due to cardiac disease, though of course it furnishes no information as to the site of the malignancy. For best results the smear should be stained by the Papanicolaou technique.

The only entirely accurate and reliable diagnostic method is histologic examination of excised tissue, which can be secured during peritoneoscopy, by aspiration biopsy, by punch biopsy, or by surgical removal of a specimen of liver at exploratory laparotomy. The chief objection to performing biopsy with peritoneoscopy is the inaccessibility of most tumors of the liver, in addition to the fact that considerable specialized training and experience are necessary for the correct use of the instruments.

Opinions differ as to the value of aspiration biopsy. It is chiefly indicated in the presence of superficial palpable masses apparently arising from the liver. Punch biopsy, however, is extremely valuable, but it is by no means free from risk. Collected reports covering 839 punctures indicate that the procedure was responsible for, or contributed to, 10 deaths, or 1.2 per cent. Gillman and Gillman,[47] who used a modification of the Iverson and Roholm apparatus, reported in 500 procedures one death from hemorrhage, which is the most usual cause of fatalities. There were no deaths in their second 500 biopsies.[48] By this method they were able to diagnose 11 cases of primary carcinoma of the liver in 42 cases of hepatomegaly due to various causes.

Volwiler and Jones[139] performed 234 biopsies with a mortality of 0.5 per cent. There were 4 hepatomas in their group; each was diagnosed correctly by punch biopsy. The method is also useful when only a nodule can be palpated. It must be remembered, however, that a negative biopsy is of no diagnostic value whatsoever, since the specimen may not have been taken from a carcinomatous portion of the liver.

Exploration.—Exploratory laparotomy is entirely justified and indeed is strongly indicated as a diagnostic measure in any case in which the diagnosis cannot be made otherwise and in which suspicion of the disease cannot be positively excluded. The most satisfactory biopsy specimens are obtained when the abdomen is open and when at the same time the exact location, size, extent, and gross characteristics of the tumor can be observed, local extension can be determined, and the possibility of metastases to regional lymph nodes or more distant structures can be evaluated. Exploration offers the patient with carcinoma of the liver his only chance of survival, and there should be no hesitancy in resorting to it promptly.

DIFFERENTIAL DIAGNOSIS

It is possible to do little more than mention the various conditions from which primary carcinoma of the liver must be differentiated. The most important is carcinoma of the stomach with hepatic metastases, with carcinoma of the transverse colon, the left colon, and the rectum next in importance. Differentiation is chiefly by roentgenography.

Primary carcinoma of the liver associated with jaundice must be differentiated from cholelithiasis, and carcinoma of the gall bladder, extrahepatic bile ducts, ampulla of Vater, and pancreas. Echinococcus cysts of the liver, which are sometimes associated with jaundice, must also be differentiated. Cardiac conditions must be excluded in cases in which dyspnea, hepatomegaly, abdominal pain, and edema of the ankles are present. If fever is prominent, hepatic abscess must be considered. Serious intra-abdominal hemorrhage in carcinoma of the liver can usually be differentiated from other acute abdominal catastrophes only by exploration. Syphilis of the liver, although extremely uncommon, is a diagnostic possibility. Gumma of the liver, which is usually confined to the left lobe, should be considered. Hepatic cirrhosis is a possibility, especially if the liver is small, though it must also be considered if the liver is large and nodular. Esophageal varices associated with a large nodular liver may be due either to primary carcinoma of the liver or to cirrhosis; they are almost never present in association with secondary hepatic carcinoma.[20]

Banti's disease, especially in children, may be manifested by jaundice, ascites, anemia, hematemesis, and splenomegaly, though, as Wentz and Kato[147] suggested, the symptom complex might better be designated Banti's syndrome, since it can occur in association with hepatic neoplasms. Benign tumors of the liver, which are not uncommon in children, can be differentiated from hepatic malignancy only by histologic investigation.

In this series of 55 cases of primary carcinoma of the liver, the correct diagnosis was made only 13 times. As in many reported series, cardiac disease with congestive failure was the most frequent diagnosis, being recorded 18 times. The clinical course of the disease is against the diagnosis, and although there may be marked edema of the feet, jugular distention is not present. In Gregory's opinion the pedal edema is more marked in primary carcinoma of the liver than is compatible with a diagnosis of cardiac disease.

Other diagnoses included cirrhosis of the liver 13 times; carcinoma of the gastrointestinal tract, especially of the stomach, with hepatic metastases 10 times; amebiasis—which the patients did not have—6 times; carcinoma of the pancreas and gumma of the liver in 4 cases each; Hodgkin's disease in 3 cases; retroperitoneal sarcoma and carcinoma of the gall bladder in 2 cases each; and, in 1 case each, Banti's syndrome, cerebral apoplexy, central nervous system syphilis, carcinoma of the lung, hydatid cyst of the liver, neurocirculatory asthenia, obstructive cholelithiasis, chronic leucemia, pancreatic cyst, hypernephroma, cystadenoma of the ovary, and carcinoma of the extrahepatic biliary tract. Most of these diagnoses, it must be granted, did not seem unreasonable.

THERAPY

The treatment of primary carcinoma of the liver is strictly surgical. In the presence of diffuse intrahepatic metastases the outlook is obviously hopeless, but in its absence surgical extirpation of the tumor should be attempted. Warvi,[143] in a review of the literature, compiled certain criteria which, in the opinion of many authorities, should be met before operation is carried out: (1) The carcinoma must be of the solitary, localized variety. (2) There must be no evident lymph node, blood vessel, or bile duct involvement at the hepatic hilum. (3) There must be no marked reduction of hepatic function. Other authorities, such as McArthur,[85] Cattell,[24] and Brunschwig,[16] are far more radical and perform extensive resections of the liver even when adjacent organs are involved or secondary deposits are known to be present.

Certain anatomic and physiologic features of the liver are favorable to resection. The free anastomosis between the right and left hepatic arteries, as Martens[83] and Mann[81] emphasized, ensure that the blood supply will be adequate if one or the other is divided. Again, the lobes and lobules are supplied by independent arteries, so that single areas may be removed without harmful consequences to the areas left in situ.

Mann's[81] extensive studies have shown that if the portal circulation is adequate and intact, restoration of hepatic tissue after partial hepatectomy is rapid and complete; in experimental animals as much as 80 per cent of the liver can be removed with safety. The same regeneration apparently occurs in human subjects, as Wendel[146] demonstrated in 1920. He found an organ of approximately normal size when he operated for the second time on a woman whose liver he had partially resected two years earlier.

Resection of the liver for both benign and malignant neoplasms has been practiced for many years. Notable contributions were made by Keen,[68] Yeomans,[158] G. Turner,[136] Wright,[156] P. Turner,[137] Kidd[71] and Abel,[1] and, more recently, by Cattell,[24] Benson and Penberthy,[5] Packard and Stevenson,[101] Pickrell and Clay,[104] and Wallace.[140] The experience with wounds of the liver in World War II furnishes further impetus to continued endeavors in the field of partial hepatectomy.

The chief difficulty encountered at operation is control of hemorrhage. Marsupialization, electrocauterization, elastic tourniquets, packs, deep interlocking mattress sutures, and temporary clamping of the main blood supply have all been employed with varying degrees of success. A useful method of controlling hemorrhage would seem to be the thrombin spray devised in 1939 by Warner, Seegers, Brinkhous, and Smith,[141] or its more convenient modern counterparts, thrombin foam, oxidized cellulose, and gelfoam.

Total extirpation of the left and caudate lobes is technically simpler when the malignant tumor occupies either of those sites than is excision of only the carcinomatous area. Mobilization is accomplished by dividing the falciform ligament near its diaphragmatic attachment, while hemostasis is carried out with two or more rows of mattress sutures of braided silk or cotton placed in the interlobar sulcus and tied on the inferior surface, after the method of Pickrell

and Clay.[104] The raw surface is then covered with the falciform ligament, while the right lobe is firmly attached to the diaphragm by figure-of-eight sutures.

None of the 55 patients reported in this communication were submitted to surgery. It seems fair to say that if the degree of clinical suspicion had been higher, if exploration had been borne in mind as a diagnostic procedure, and if it had been remembered that no patient with carcinoma of the liver has any chance of survival without surgery, the outcome in at least a few of these cases might have been different.

Postoperative Complications.—Possible postoperative complications include hemorrhage, hepatic abscess, peritonitis and ileus, respiratory complications, sinus formation with discharge of bile, hematemesis (from engorgement of the portal circulation as the result of clamping the hepatoduodenal vessels at operation), and such metabolic disturbances as liver shock, hepatic hypoglycemia, and the hepatorenal syndrome.[143] They are seldom troublesome. It is of interest that to date no case seems to have been reported in which the so-called liver death or hepatorenal syndrome occurred after resection of a primary carcinoma of the liver.

PROGNOSIS AND END RESULTS

All experience indicates that primary carcinoma of the liver is a rapidly fatal disease. Few patients live more than four to six months after the first clinical manifestations appear. In this series the duration of life from the onset of symptoms to death ranged from 4 days to 13 months and averaged 2.8 months. Eighty-two per cent of the patients were dead within 6 months, 61 per cent within 3 months, and 21 per cent within 1 month after they first became aware of the illness.

The incidence of metastases varied with the duration of life after the onset of symptoms. The more rapid the course, the fewer the metastases. The average duration of life in 29 patients with liver cell carcinoma was 4.6 months and the incidence of metastases in this group was 79.3 per cent. Thirteen patients with bile duct cell carcinomas lived on an average of 2.7 months after the onset of symptoms and presented an incidence of metastases of 69.2 per cent, while the respective figures for five mixed cell tumors were 1.2 months and 40 per cent. These figures parallel those reported by Warvi:[143] His 22 patients with hepatomas lived on an average of 8 months after the onset of symptoms, while in 9 patients with cholangiomas, the duration of life was only 6 weeks.

Tinker and Tinker, Jr.,[133] have properly pointed out that unfavorable results following partial resection of the liver for carcinoma are based upon the statistics of operations performed early in this century. Recent advances in preoperative and postoperative care, especially in respect to transfusion and other replacement therapy, improvements in anesthesia and surgical technique, and the introduction of chemotherapy and antibiotic therapy have made hepatectomy, like many other operations which were formerly extremely hazardous, reasonably safe procedures. There is general agreement that recurrences following operation can usually be attributed to inadequate removal of neoplastic tissue.

The large number of resections of the liver collected from the literature by Warvi[143] is not useful for the purposes of this communication because the distribution into benign and malignant cases is not entirely clear. Wallace's[140] collected statistics, though the series is not large, can probably be assumed to be typical of present-day results: Of 29 patients with resectable hepatomas, 23 survived operation. Eight of 20 patients upon whom follow-up studies were done were known to have recurrences, but 12 were known to be alive and well for periods ranging from two to five years after operation. Of 16 cases collected by Yeomans,[158] 4 patients died after operation, 6 developed recurrences at various times, but 6 were alive and well at intervals varying from three to seven years. When one considers that without surgery carcinoma of the liver is 100 per cent fatal, even higher mortalities and even higher recurrence rates would not seem prohibitive. The statistics, in fact, warrant more frequent attempts at resection, removal of localized tumors, or complete lobectomy, since surgery alone offers the patient the only chance for survival.

REPORT OF CASE

A 54-year-old white man was seen at the Ochsner Clinic July 14, 1947, with the chief complaints of indigestion and "a mass in the stomach." Four months earlier, while at his usual (manual) work, he had a sudden, severe, colicky pain in the epigastrium, which was not relieved by bicarbonate of soda but which subsided spontaneously after a few hours' rest. Two months later he was awakened from sleep by a severe "pulling" pain in the epigastrium, which again subsided after rest. During this attack, however, he was more comfortable in the sitting position. Six weeks later (that is, two weeks before he sought medical consultation) he was again awakened from sleep by a severe, colicky epigastric pain. Again he was more comfortable in a sitting position. This time the pain did not disappear completely for three or four days and during this attack he noticed for the first time a small mass in the epigastrium.

Except for a history of recent fatigue, especially during the three weeks before he was first seen, the patient had no other symptoms of any kind. He had lost no weight. Past history, family history, and a review of symptoms revealed nothing significant.

Physical Examination.—The patient was a rather thin adult, weighing 125 pounds, who did not seem in ill health. Examination was essentially normal except for the abdominal findings. A visible mass, about 7 cm. in diameter, was present in the epigastrium. Palpation revealed it to be tender, of firm consistency, and slightly mobile. It moved on respiration. The pulsations of the aorta were readily transmitted through it. It seemed to lie just beneath the anterior abdominal wall and was thought to be attached to the liver, the edge of which was barely palpable. No other masses could be palpated in the abdomen.

Laboratory Data.—Urinalysis and blood serology were negative. The red blood cell count was 4,850,000 and the white blood cell count 9,900 per cu. mm. The hemoglobin was 15.2 Gm. per cent. The blood amylase was 55 mg. per cent. The sedimentation rate was 4 mm. in one hour. The cephalin flocculation test was 1 plus and the bromsulfalein excretion test showed 1 per cent retention in 45 minutes. The urea clearance test showed 75 per cent excretion in 2 hours. Stool examination showed *Giardia lamblia*. The glucose tolerance curve was normal.

Other Tests.—Roentgenologic examination of the chest, gall bladder, and upper gastrointestinal tract and intravenous pyelogram revealed no abnormalities. The electrocardiogram also revealed no abnormalities.

Preoperative Diagnosis.—Preoperative diagnosis considered included primary carcinoma of the liver, hemangioma of the liver, and pancreatic cyst with hemorrhage. The first diagnosis, carcinoma of the liver, was considered most reasonable. The attacks of pain were explained on the basis of hemorrhage into the tumor.

Operation.—Operation was carried out August 8 by one of us (A. O.). The abdomen was opened through a transverse upper abdominal incision. The only abnormal finding, after a thorough search of all portions of the peritoneal cavity for another possible primary site, was a tumor mass measuring about 7 cm. in diameter in the left lobe of the liver. Frozen section confirmed the preoperative diagnosis of primary carcinoma (liver cell) of the liver. Resection of the left lobe was carried out. Through-and-through overlapping mattress sutures of chromic No. 2 catgut were passed through the liver at the site of division between the lobes and were drawn taut but not tied. The left lobe of the liver, with the tumor in situ, was resected with a scalpel. The sutures already placed were then tied on the superior surface and additional sutures were placed at individual bleeding points. The raw surface was covered with the falciform ligament. The anterior abdominal wall was closed in layers, with sutures of quilting cotton and No. 80 cotton. (Refer to Fig. 1.)

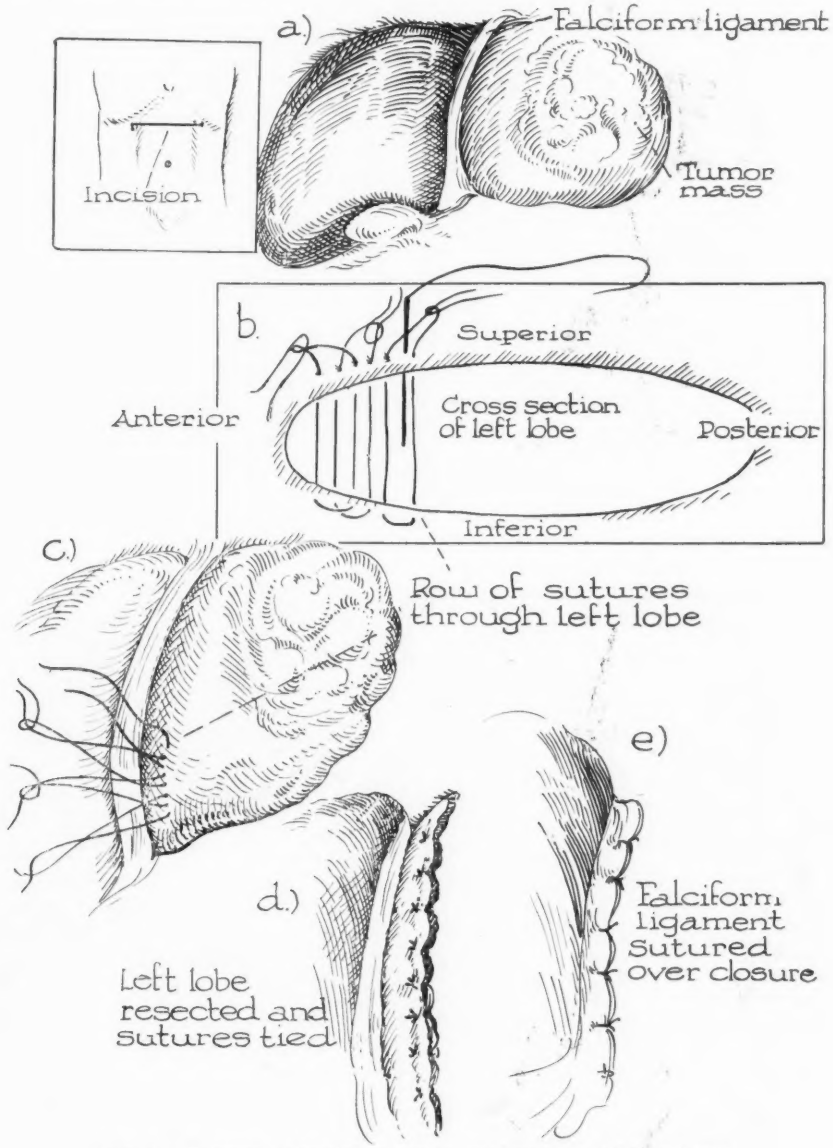

Fig. 1.—Diagram showing steps in performance of lobectomy.

The patient was given 1,500 c.c. of blood during the operation and was returned to the ward in good condition. Bleeding had been slight.

Postoperative Course.—Six hours after operation the patient sustained a complete wound disruption. Under general anesthesia and tubocurarine, closure was effected by through-and-through sutures of No. 10 crochet cotton placed at 2 cm. intervals. During the next 72 hours the abdomen became greatly distended with fluid, and on the fifth day after operation a second wound disruption occurred. The wound was again closed under general anesthesia in the same fashion as after the first disruption.

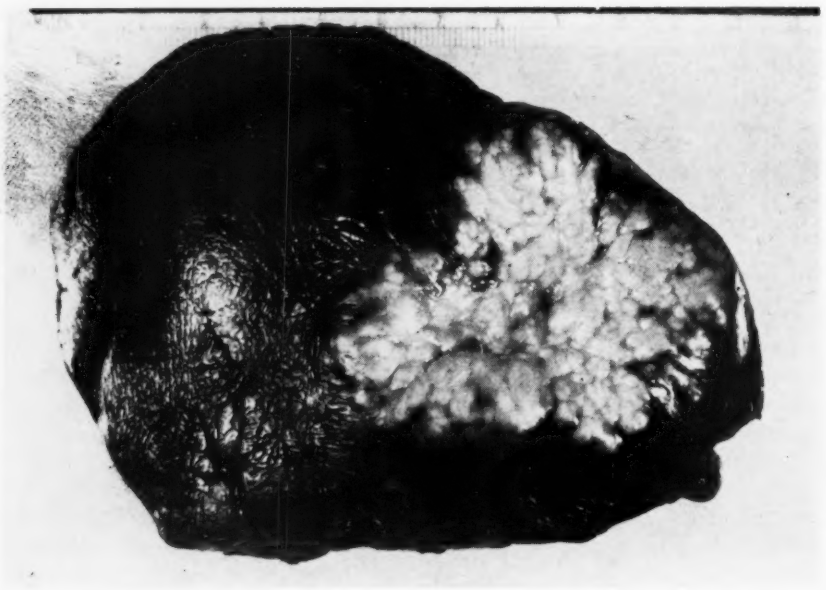

Fig. 2.—Photograph of tumor and resected left lobe of liver.

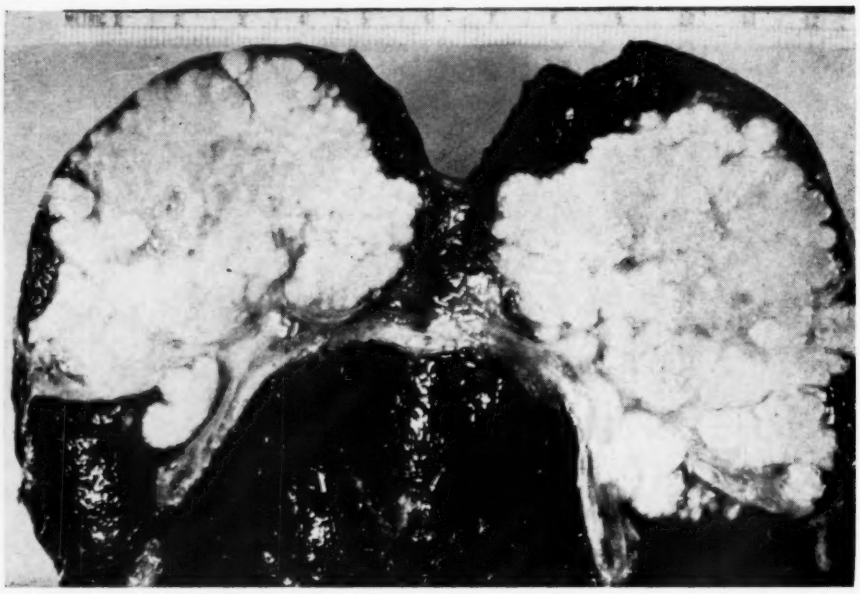

Fig. 3.—Photograph showing extent of tumor in resected left lobe of liver.

The subsequent postoperative course was relatively uneventful. The patient was allowed out of bed August 24 and was discharged in good condition three days later.

Pathologic Report.—The specimen, which consisted of the left lobe of the liver, weighed 230 Gm. On its lower margin was a mass 5.5 by 6.5 cm., lobulated and faintly yellow. The surrounding parenchyma appeared normal (refer to Figs. 2 and 3).

Sections of the tumor showed numerous indistinct lobules of neoplastic cells, which were compactly arranged and generally polygonal. Their nuclei were large, vesicular, and hyper-

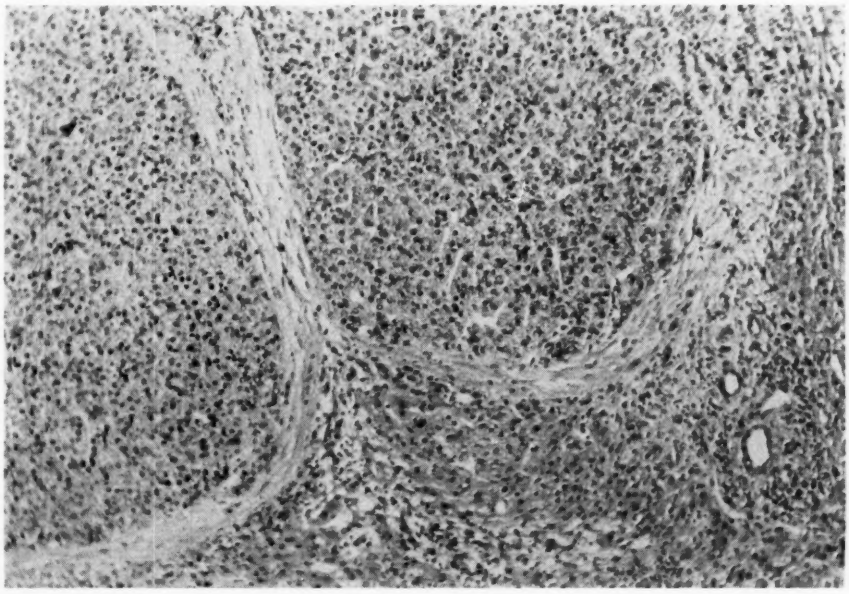

Fig. 4.—Photomicrograph showing proliferating edge of tumor separated from hepatic tissue by compression capsule. (Hematoxylin and eosin, ×100.)

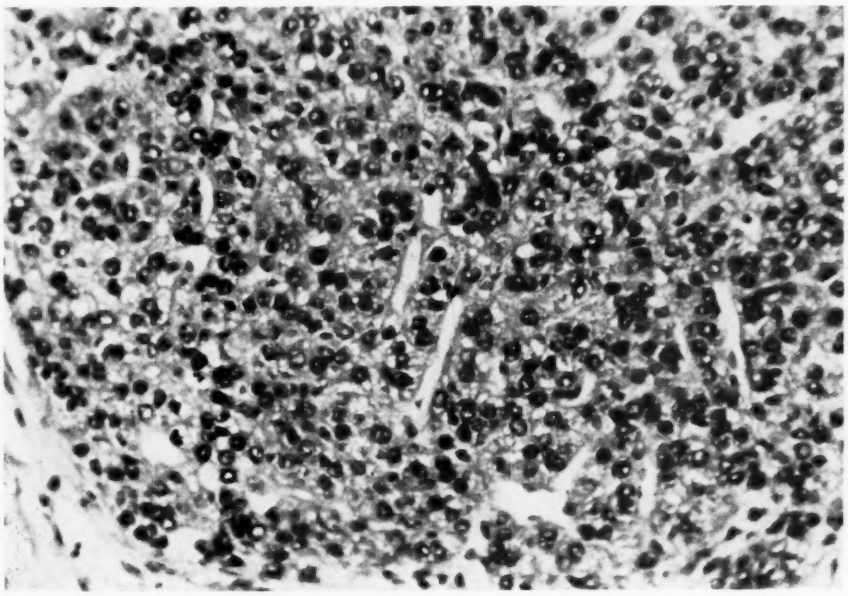

Fig. 5.—Photomicrograph showing higher power view of same area as Fig. 4. (Hematoxylin and eosin, ×200.)

chromatic. Mitosis was fairly frequent. The cytoplasm of the cells was granular. In some areas a thin trabeculation of fibrous tissue separated the tumor cells into discrete nests or cords (refer to Figs. 4, 5, and 6).

The microscopic diagnosis was primary liver cell carcinoma.

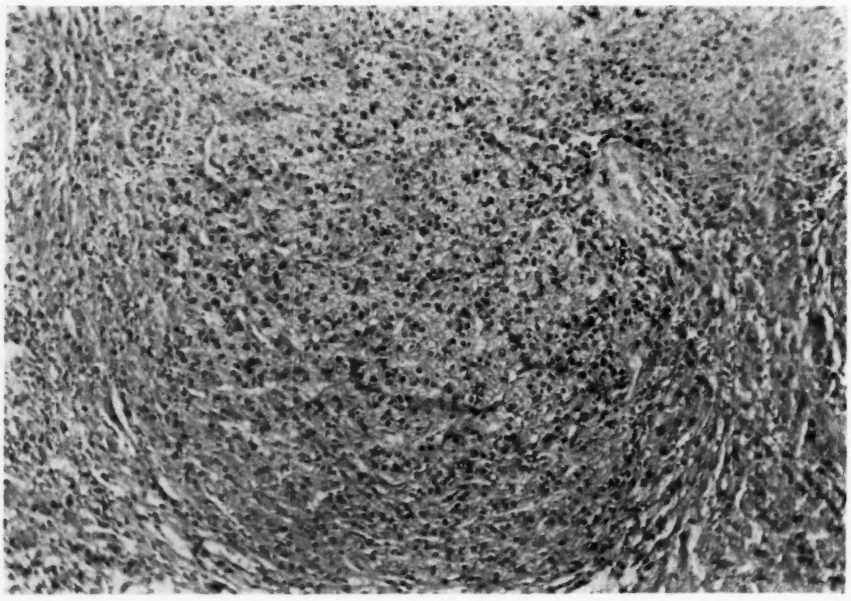

Fig. 6.—Photomicrograph showing proliferating edge of tumor, poorly defined from hepatic tissue. (Hematoxylin and eosin, ×100.)

SUMMARY AND CONCLUSIONS

Against a background of 55 histologically proved cases of primary carcinoma of the liver collected from two New Orleans hospitals, the disease has been discussed from the standpoint of incidence, etiology, clinical manifestations, pathology, diagnosis, and therapy.

The diagnosis of primary carcinoma of the liver is not easy because the clinical picture is not pathognomonic and is often vague and obscure.

The disease is rapidly fatal, the course, without surgical treatment, being measured in months. Every possible diagnostic means should therefore be employed, and exploratory laparotomy should be resorted to without delay if the suspicion of primary carcinoma of the liver is aroused and cannot positively be excluded otherwise. Surgery, with complete excision of the tumor, offers the only hope for survival, and should be undertaken without delay unless the case is clearly hopeless.

In view of the uniformly lethal outcome without surgery, the mortality and the rate of recurrence reported after operation do not seem unduly high.

An instance of successful resection of primary carcinoma of the liver is recorded.

In addition to the 55 autopsied cases of primary carcinoma of the liver reported in this communication, 98 other cases of the disease were collected from the records of Charity Hospital. They were diagnosed by other methods, in-

cluding, in 26 cases, histologic examination of a biopsied specimen secured at exploratory laparotomy. These cases will be reported in another communication.

It is our pleasure to express our sincerest gratitude to Miss E. McFetridge for her invaluable criticism and help in the preparation of this publication.

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